Keira P. Mason *Editor*

Pediatric Sedation Outside of the Operating Room

A Multispecialty International Collaboration

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This book is primarily dedicated to my mother and father, whose sacrifice, love, and encouragement enabled me to pursue my goals and dreams. Leading by example, they showed me to persevere, remain positive, optimistic, and to always strive to achieve my personal best. I thank my husband, Ed, for continuing in my parents' footsteps of encouragement, love and support. Finally, thanks to God for the gift of Tyler and Colin, my sons whom I can only hope to guide, nurture, and provide for as my parents did for me.

Preface

I am honored to present this book as a representation of the passion and expertise of all the contributing authors who are committed to the field of pediatric sedation. *Pediatric Sedation Outside of the Operating Room: A Multispecialty International Collaboration* is intended to represent all specialties from around the world. The authors represent some of the many leaders throughout all the specialties, both in the United States and abroad, in the field of sedation. I am very appreciative of their efforts. Each chapter has been revised and edited a minimum of three times (some as many as eight) and I extend a sincere "thank you" to each author.

This book represents a unique contribution to the field. It is the first book which is directed to all specialties and which specifically acknowledges and reviews the contributions and viewpoints of international societies and specialists. Sedation has evolved to include all specialties. Each chapter is written by a specialist in that particular area and intended to be of value to all sedation providers. For example, even the emergency medicine physician will learn something in the *Sedation of Pediatric Patients for Dental Procedures* chapter, which he will be able to apply or consider in his practice.

Each clinically-oriented chapter concludes with case studies, which present challenging clinical scenarios. This is a unique finale as it is the author's presentation of real-life cases. The intent of these case studies is to guide the reader through the challenges, thought process, and management options for each situation. Certainly there are many possible solutions to each scenario; exploring them through the eyes of the experienced author offers a unique and valuable perspective.

This book may be read cover-to-cover or read a chapter at a time, out of succession. There is intentional, albeit minimal, repetition in the book. The repetition is intended not only to solidify important information for the reader but also to convey relevant information for those who may not be reading the book cover-to-cover. Even the "repetition" is presented in a different style by the individual authors, in most cases masking the repeated elements.

This book went to the publisher in September 2011. Every chapter was updated the first week of September, complete with any recently published papers. Drs. Roelofse, Leroy and Sury were even so generous to share their specialty guidelines, each of which are detailed in this book but had not even been published at the time this book went to press. Dr. Thomas shared his propofol outcome data and protocols in Chap. 12: *The Anesthesia Directed*

Sedation Service: Models, Protocols, and Challenges, again prior to being published elsewhere. Even the emergency medicine update of the Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation as well as the American College of Emergency Medicine Physicians updated Procedural Sedation and Analgesia in the Emergency Department: Recommendations for Physician Credentialing, Privileging, and Practice was included. This policy will be published in October 2011.

This book represents collaboration between multiple specialists all over the world. Currently the field of sedation is being challenged by politics, differing viewpoints, and our inability to reach a consensus. Our ability to come together, outside of this book, will be essential to the future of our pediatric patients who receive sedation.

There will continue to be new clinical and research studies which contribute to our knowledge of sedation. There may, in the far future, be new sedatives which come to market. However, the approach to sedation and the information conveyed in these chapters is intended to distinguish this book as a timeless relic which marks an important era in the field of sedation.

Boston, MA
August 2011

Keira P. Mason, MD

Acknowledgments

I cannot offer this book without acknowledging my family. Thanks to my husband, Ed, and my two sons, Colin and Tyler, for bearing with the numerous "motherless" weekends and evenings as I worked on this project. I especially thank my son Tyler, who kept me company and read over my shoulders, trying to help me as I edited and revised chapters on many occasions. Likewise, I am grateful for the companionship of my younger son Colin, as he sat next to me during many late nights in order to offer encouragement, keep me awake and ask me "do you need help?"

I would like to express my respect, gratitude, and appreciation to Shelley Reinhardt, Senior Editor in Clinical Medicine and Portia Levasseur, Developmental Editor of Springer. Their encouragement, gentle prodding, attention to detail, kindness, expertise, and professionalism inspired me to meet all deadlines. Most importantly, they were committed to this project: Committed to supporting all efforts to produce Pediatric Sedation Outside of the Operating Room as a contribution to the field.

My final and most important acknowledgement is to Ms. Amanda Buckley, the clinical coordinator and administrator who committed herself for the past 3 years to this project. From the inception of this book to the final moment of galley proof approval, she devoted even the after-hours to ensuring that all

references and source information were accurate, the grammar and typos corrected, the copyrights were obtained, and that everything from the table of contents to the final chapter flowed appropriately. Her commitment and belief in this project inspired me to drive this book to completion. She has read this book cover-to-cover more than once. I will always be appreciative.

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Part I

Pediatric Sedation Outside the Operating Room

The History of Sedation

1

Robert S. Holzman

The history of induced altered states as a means of tolerating the intolerable is as old as man and for eons has been associated with a loss of self-control alternately welcomed, worshipped and vilified [1]. Ironically, as in ancient times, these three attitudes often coexist, and our professional duty is to care for and educate our patients and public, controlling the end-effects while minimizing the risks, therefore enhancing the safety [1–3].

Is the history of sedation different from the history of anesthesia? They were, and often continue to be, inseparable, particularly for children [4]. This chapter will focus on the various modalities and practices over time, emphasizing the differences but remaining in awe of the similarities through the ages.

Ancient History

The emperor Shennung (2737–2697 Before the Common Era, BCE) made the earliest systematic study of herbal medicine. The Shennung Herbal (c. 200 BCE) mentioned the medicinal uses of 365 drugs, including the opium poppy, *Papaver somniferum*, for pain relief [5].

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The Sumerians codified many of their practices on at least 800 of 30,000 clay tablets from the time of Ashurbanipal of Assyria (568–626 BCE) [6]. Beers were an especially well-developed intoxicating drug in Babylon; hemp (*Cannabis indica*) was a well-acknowledged agent, producing ecstasy and exaltation, and was also recognized as a minor pain-relieving agent. Jewish potions were prepared by the priesthood for pain relief and the imparting of sleep during surgical procedures, venesection and leeching; *Samme de shinda* was probably a hemp potion [7].

The Charaka and Susruta, Hindu medical documents thought to have been written about 1,000 BCE, describe the use of wine and fumes of hemp "to produce insensibility to pain." There were over 700 medicinal plants detailed in the Susruta, including the depressant effects of *Hyoscyamus* and *Cannabis indica* [6].

Classical History

Greek Medicine

Chaldo-Egyptian magic, lore and medicine was transferred to the coasts of Crete and Greece by migrating Semitic Phoenicians or Jews and the stage was then set for incorporating ancient Egyptian drug lore into Greek medicine. Two prominent medical groups developed on the mainland of Asia Minor: the group on Cnidos, which was the first, and then the group on Kos, of which Hippocrates

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(460–380 BCE) was one member. While they were accomplished surgeons, they generally eschewed drugs, believing that most sick people get well regardless of treatment. Although Hippocrates did not gather his herbal remedies, he did prescribe plant drugs, and a cult of root diggers (*rhizotomoi*) developed, as did a group of drug merchants (*pharmacopuloi*). In Greece, plants were used not only for healing but also as a means of inducing death, either through suicide or execution; perhaps the best example was the death of Socrates.

Later, Theophrastus (380–287 BCE), a pupil of Aristotle (384–322 BCE), classified plants and noted their medicinal properties. This was a departure from previous recordings, as Theophrastus analyzed remedies on the basis of their *individual* characteristics, rather than a codification of combinations as in Egyptian formularies. He provided the earliest reference in Greek literature to mandragora [8].

Roman Medicine

After the decline of the Greek empire following the death of Alexander the Great (323 BCE), Greek medicine was widely disseminated through the Roman Empire by Greek physicians, who often were slaves. Dioscorides described some 600 plants and non-plant materials including metals. His description of mandragora is famous – the root of which he indicates may be made into a preparation which can be administered by various routes and will cause some degree of sleepiness and relief of pain [9]. In the first century, Scribonius Largus compiled *Compositiones Medicorum* and gave the first description of opium in Western medicine, describing the way the juice exudes from the unripe seed capsule and how it is gathered for use after it is dried. It was suggested by the author that it be given in a water emulsion for the purpose of producing sleep and relieving pain [6]. Galen (129–199 CE), another Greek, in *De Simplicibus* (about 180 AD), described plant, animal, and mineral materials in a systematic and rational manner. His prescriptions suggested medicinal uses for opium and hyoscyamus, among others; his formulations became known as galenicals.

Islamic Medicine

In 640 CE, the Saracens conquered Alexandria, Egypt's seat of ancient Greek culture and by 711 CE they were patrons of learning, collecting medical knowledge along the way. Unlike the Christians, who believed that one must suffer as part of the cure, the Saracens tried to ease the discomfort of the sick. They flavored bitter drugs with orange peels and sweets, coated unpleasant pills with sugar, and studied the lore of Hippocrates and Galen. They translated Greek texts into Syriac and spread the knowledge of Hellenic culture throughout the East. Persian physicians became the major medical teachers after the rise of the Baghdad Caliphate around 749 CE, with some even penetrating as far east as India and China. By 887 there was a medical training center with a hospital in Kairouan in Northern Africa.

The most prominent of the Arab writers on medicine and pharmacy were Rhazes (865–925 CE) and Avicenna (930–1036 CE), whose main work was *A Canon on Medicine*. The significance of this thread of ancient medical philosophy was that during the eleventh and twelfth centuries, this preserved knowledge was transmitted back to Christian Europe during the Crusades. Avicenna recognized the special analgesic and soporific properties of opium, henbane, and mandrake [10] (Fig. 1.1).

Medieval Medicine

The first Christian early medieval reference to anesthesia was found in the fourth century in the writings of Hilary, the bishop of Poitiers [11]. In his treatise on the Trinity, Hilary distinguished between anesthesia due to disease and "intentional" anesthesia resulting from drugs. While St. Hilary does not describe the drugs that lulled the soul to sleep, at this time (and for the following few centuries) the emphasis remained on mandragora.

3BFrom 500 to 1400 CE the church was the dominant institution in all walks of life, and medicine, like other learned disciplines, survived in

Fig. 1.1 Avicenna (930–1036 CE) "If it is desirable to get a person unconscious quickly, without his being harmed, add sweet-smelling moss or aloes-wood to the wine. If it is desirable to procure a deeply unconscious state, so as to enable the pain to be borne, which is involved in painful application to a member, place darnel-water into the wine, or administer fumitory opium, hyoscyamus (half dram dose of each); nutmeg, crude aloes-wood (4 grains of each). Add this to the wine, and take as much as is necessary for the purpose. Or boil black hyoscyamus in water, with mandragora bark, until it becomes red, and then add this to the wine." [10]

Western Europe between the seventh or eighth and eleventh centuries mainly in a clerical environment. However, monks did not copy or read medical books merely as an academic exercise; Cassiodorus (c. 485–585), in his efforts to bring Greek learning to Latin readers and preserve sacred and secular texts, recommended books by Hippocrates, Galen, and Dioscorides while linking the purpose of medical reading with charity care and help. Therefore, while preserved, the herbal of Dioscorides was accorded blind acceptance as the authoritative source on medical plants for virtually the entire 1,000-year interregnum of the Dark Ages.

Conventional Greco-Roman drug tradition, organized and preserved by the Muslims, returned to Europe chiefly through Salerno, an important trade center on the southwest coast of Italy in the mid 900s. Since an increasing number of monks now spent more time pursuing their medical aims and less time fulfilling their religious duties, medical practice and reliance on medicine were taking on a more secular and specialized caste. Salerno's medical melting pot was a hub of knowledge derived from sources as diverse as the ancient Greco Roman tradition (still present in southern Italy), monastic medicine, and Jewish, Arabic and Oriental practices of the Middle East and Northern Africa [12]P.

One of the more impressive practices documented at Salerno was intentional surgical anesthesia, described in *Practical Chirugiae* in 1170 by the surgeon Roger Frugardi (Roger of Salerno), in which he mentions a sponge soaked in "narcotics" and held to the patient's nose. Hugh of Lucca (c. 1160–1252) prepared such a sleeping sponge according to a prescription later described by Theodoric of Cervia (c. 1205–1296). As an added precaution, Theodoric bound his patients prior to incision. The description of the soporific sponge of Theodoric survived through the Renaissance largely because of Guy de Chauliac's (1300–1367) *The Grand Surgery* and the clinical practices of Hans von Gersdorff (c. 1519) and Giambattista della Porta (1535–1615), who used essentially the same formula of opium, unripe mulberry, hyoscyamus, hemlock, mandragora, wood-ivy, forest mulberry, seeds of lettuce, and water hemlock (Fig. 1.2).

Ether

Ether was discovered in 1275 CE by the Spanish chemist Raymundus Lullius. This new discovery was given the name "sweet vitriol." In 1540 CE, the synthesis of ether was described by the German scientist Valerius Cordus (1514–1544 CE) who carefully specified the materials to be used, the apparatus, and the procedure to be followed in order to distil "strong biting wine" (alcohol) with "sour oil of vitriol" (sulfuric acid). This was

Fig. 1.2 The alcohol sponge [22]. "Take of opium, of the juice of the unripe mulberry, of hyoscyamus, of the juice of hemlock, of the juice of the leaves of mandragora, of the juice of the wood-ivy, of the juice of the forest mulberry, of the seeds of lettuce, of the seeds of the dock, which has large round apples, and of the water hemlock - each an ounce; mix all these in a brazen vessel, and then place in it a new sponge; let the whole boil, as long as the sun lasts on the dog-days, until the sponge consumes it all, and it is boiled away in it. As oft as there shall be need of it, place this sponge in hot water for an hour, and let it be applied to the nostrils of him who is to be operated on, until he has fallen asleep, and so let the surgery be performed. This being finished, in order to awaken him, apply another sponge, dipped in vinegar, frequently to the nose, or throw the juice of the root of fenugreek into the nostrils; shortly he awakes." [23]

a far leap from the conventional secrecy and esoteric rites of the alchemists. Thinking the product to be liquid sulfur, he noted its lack of color, its rapid evaporation, its tendency to cause salivation, and its safety. He recommended it for the relief of cough and pneumonia [13]. Paracelsus (1493–1541), a contemporary of Cordus, came surprisingly close to the recognition of ether as an anesthetic [14]. Later, in 1730, German scientist W.G. Frobenius changed the name of sweet vitriol to ether.

Varied Preparations of Varying Potencies

If the constituents of the plants were combined with fats or oils, they would penetrate through the skin or could be easily absorbed via the sweat ducts in the axillae or body orifices such as the vagina or rectum. This would allow the psychoactive tropane alkaloids, especially hyoscine, access to the blood and brain without passage through the gut, thus avoiding the risk of

Fig. 1.3 John Arderne (1307–1380) "An ointment with which if any man be anointed he shall suffer cutting in any part of his body without feeling or aching. Take the juice of henbane, mandragora, hemlock, lettuce, black and white poppy, and the seeds of all these aforesaid herbs, if they may be had, in equal quantities; of Theban poppies and of poppy meconium one or two drachms with sufficient lard. Braize them all together and thoroughly in a mortar and afterwards boil them well and let them cool. And if the ointment be not thick enough add a little white wax and then preserve it for use. And when you wish to use it anoint the forehead, the pulses, the temples, the armpits, the palms of the hands and the soles of the feet and immediately the patient will sleep so soundly that he will not feel any cutting." [24, 25]

Fig. 1.4 Andres de Laguna (1499–1560 CE) " … a pot full of a certain green ointment … with which they were annointing themselves … was composed of herbs … such as hemlock, nightshade, henbane, and mandrak … I had the wife of the public executioner annointed with it from head to foot … she … had completely lost power of sleep … no sooner did I annoint her than she opened her eyes, wide like a rabbit, and soon they looked like those of a cooked hare when she fell into such a profound sleep that I thought I should never be able to awake her … after a lapse of 36 h, I restored her to her senses and sanity." [26]

poisoning. A few prominent surgeons offered statements about the mode of application of such salves or "oyntments." John Arderne (1307–1380), known for his success curing fistula in anus, and Andres De Laguna (1499–1560), physician to Emperor Charles V and Philip II, provided unambiguous descriptions of soporifics (Figs. 1.3 and 1.4).

The Transitional Epoch-Secular and Non-Secular Ambivalence and the Mistrust of Drugs

The uncertainly of the potency and action of the narcotic drugs rendered their application dangerous and by the end of the sixteenth century such anesthetics had largely fallen into disuse. Indeed, even if physicians tried to use "narcotic" herbals in the middle of the seventeenth century, they were condemned, arrested, and fined or tried for practicing witchcraft [15]. Many of the early books were herbals, and Gerard (1545–1612) warned of the

alkaloids "… this kind of Nightshade causeth sleepe … it bringeth such as have eaten thereof into a ded sleepe wherein many have died" [16].

The Scientific or Modern Epoch

The divergence of herbalism (botany) and medicine began in the seventeenth century as part of the larger movement known alternatively as natural philosophy, scientific deism, and the scientific revolution. An attempt to develop quantitative methodology characterized science, and at the forefront of these attempts was the chemical analysis of the active ingredients in medicinal plants.

Following his clinical observation of poisoning in children who had mistaken water hemlock for parsnip root, Johann Jakob Wepfer (1620–1695) demonstrated dose-dependent toxic effects in dogs of the alkaloids eventually isolated as strychnine, nicotine, and conine [17, 18]. Thus, this early quantitative approach gave rise to the development of modern chemistry and pharmacology. This was first successfully applied to anesthetic pharmacology by Friedrich Wilhelm Adam Serturner (1783–1841) who, in 1805, described the isolation of meconic acid from the crude extract of opium and in 1806, extracted opium. He further experimented with this crystal on dogs, finding that it caused sleep and indifference to pain and called this new substance morphine, in honor of the Greek god of dreams, Morpheus. This science of pharmacology – the interaction of chemistry with living matter – thus began to replace the ancient and descriptive materia medica of herbalism, and set the stage for the advances of the second half of the nineteenth century, which included modern surgical anesthesia.

The Modern Story of Anesthesia

The modern story of anesthesia began with the reaction in Philadelphia to Humphrey Davy's (1778–1829) account of nitrous oxide and its biological effects. In 1808, William P.C. Barton (1786–1856) emphasized the brain disorientation caused by inhaling nitrous oxide, and cited Davy. Meanwhile, an anonymous note, often ascribed to Michael Faraday, indicated that the inhalation of ether would produce effects similar to those of nitrous oxide [19].

In 1839, William E. Clarke (1818–1878) in Rochester, NY began the fad of ether frolics among young people. He is said to have given ether for extraction of a tooth in 1842. In Jefferson, GA, Crawford W. Long (1815–1878) noted that one of the participants in an ether frolic fell heavily, but seemed to lack pain. On March 30th, 1842, Long gave ether by inhalation to a patient for removal of a neck tumor; there was no evidence of pain. Unfortunately, he failed to report his anesthetic success for several years. William T.G. Morton (1819–1868), a student at Harvard Medical School, learned of sulfuric ether, and practiced anesthetizing various small animals at his home. He tried to perfect an inhaling device, and a demonstration was arranged at the Massachusetts General Hospital on October 16PthP, 1846, a turning point in the history of medicine. Gardner Quincy Colton (1814–1898) first gave nitrous oxide for anesthetic purposes to Horace Wells in 1844 and revived its use in dentistry for dental extractions in 1863. Alfred Coleman (1828–1902) became the chief advocate for the use of nitrous oxide in dentistry.

There were additional "sleep-producing" agents available in the second half of the nineteenth century. For example, it was recognized by Robert Glover that potassium bromide would cause drowsiness in animals and by Charles Locock that it would effectively treat epileptic seizures in obstetrical patients being treated for dysmenorrheal. Behrend reported its use for the treatment of insomnia, nervous excitement, and irritability. This led to the therapeutic use of "bromides" (of lithium, sodium and potassium) as anticonvulsants. It was only a short time later that chloral hydrate was introduced by Liebreich as a soporific for medical purposes [20], as well as for more nefarious purposes (it was the chief ingredient in the "Micky Finn" cocktail, for which the bartender, Michael Finn, was tried in 1903 in Chicago). Additional soporifics were paraldehyde, ethanol, sulphonal, diethyl-malonyl-urea (Veronal, or barbital), and phenyl-ethyl-malonylurea (Luminal, or phenobarbital).

Following its introduction and promotion as a short-acting intravenous dissociative anesthetic in 1962, ketamine became a favorite for anesthetics administered outside of the operating room; it avoided the appearance of general anesthesia while providing motionlessness and analgesia (in anesthetic doses). Frequent practitioners of the technique quickly noted that tachyphylaxis developed after only a few administrations in most patients requiring serial sedations, for example, for radiation therapy. This prompted a variety of pharmacologic strategies that were ultimately replaced when propofol was introduced in 1989.

"Modern" Sedation and Analgesia Services

There is an inseparable continuum, particularly in pediatrics, between general anesthesia and sedation and analgesia. Not surprisingly, it was the early efforts of dental surgeons at the beginning of the twentieth century that spearheaded ambulatory anesthesia, as early general anesthesia was associated with dental procedures. Ralph Waters (1883–1979) opened the Downtown Anesthesia Clinic in Sioux City, Iowa in 1916, caring for dental and minor surgery patients! Intermittently, pediatric anesthesiologists filled the role of sedation experts in order for children to tolerate unpleasant diagnostic procedures (Fig. 1.5). Nevertheless, Waters' prescience was followed by a long gap, until the 1960's, when increasing interest in employing shorter-acting anesthetic strategies with more rapid return to "street-fitness" predated the explosion onto the medical diagnostic scene of computed tomography (1974), magnetic resonance imaging (1977), interventional radiology procedures, cardiac catheterization (diagnostic and interventional), and various other imaging modalities. In addition, further miniaturization and engineering improvements continued for both gastrointestinal and pulmonary endoscopy and the use of radiation therapy as an adjunct to surgical and medical treatment of cancer patients. All of these took place in nontraditional anesthetizing locations, popularly known as "outfield" anesthesia [21]. These services, which often require sedation and analgesia or general anesthesia, occupy such a large (and increasing) fraction of pediatric anesthesia practice that at Children's Hospital Boston we currently provide such services for more than 9,000 procedures per year (Table 1.1).

Table 1.1 Anesthesia encounters (sedation and general anesthesia) outside the operating room

Children's Hospital Boston	2010
Interventional radiology	2,000
Cath Lab	1,500
Diagnostic radiology (CT, MRI)	3,899
Gastrointestinal endoscopy	1,450
Oncology	540
Radiation therapy	368
Total	9,757

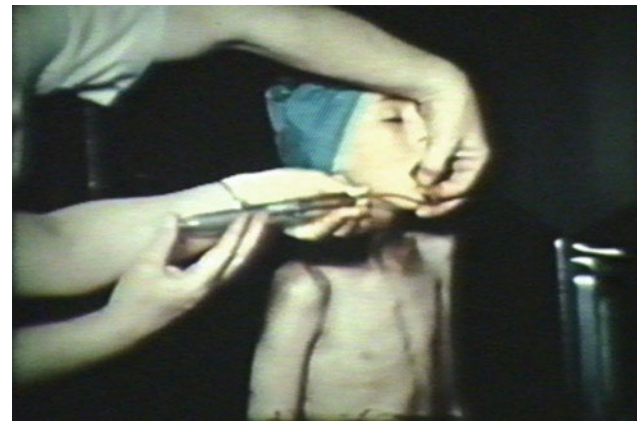

Fig. 1.5 A cachectic child undergoing intrapulmonary contrast injection via an intratracheal catheter for radiographic evaluation of tuberculosis. (From a pediatric anesthesia training film made by Dr. M. Digby-Leigh in 1947)

The Future of Sedation

As an increasing number of procedures are developed that are accessible by percutaneous, intravascular or natural orifice routes, they will be less painful in both the awake and asleep state. However, the need for motionless conditions for children as well as adults will remain, especially as these imaging techniques and procedures are likely to be longer and require increasingly sophisticated instrumentation. At the same time, progress will inevitably continue in understanding the neurophysiology of pain mechanisms as well as consciousness, and we are perhaps not that far removed from the "tricorder" settings in Star Trek to noninvasively control mediators of pain, attention, and neuromuscular competence, all in scalable fashions.

Anesthesia and sedation in the absence of surgery is not a new idea; indeed, it is an idea that has persisted through the eons and is likely to evolve exponentially as our diagnostic procedures and interventions become more sophisticated and our knowledge about neurophysiology grows.

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Procedural Sedation: Let's Review the Basics – The Pediatrician's Perspective

2

Vincent W. Chiang

For the welfare of children

–Motto, American Academy of Pediatrics

Pediatricians, by their very nature, are patient advocates. As such, it is no wonder that pediatricians have taken a leadership role in trying to define standards around the management of pain, anxiety, and motion in children undergoing medical procedures. In 1985, the American Academy of Pediatrics published its first set of guidelines for the elective use of conscious sedation. These guidelines have continued to evolve over the last 20-plus years [1]. In this time, our understanding of pediatric pain experiences as an interplay of genetic, experiential and developmental factors has grown considerably [2, 3]. Simultaneously, the widespread availability of noninvasive monitoring, short-acting opioids and sedatives, and specific opioid and benzodiazepine antagonists has greatly increased our ability to provide procedural sedation in a wide array of practice settings [4].

The practice of procedural sedation, however, is not simply the administration of pharmacologic agents to remove all pain. In every clinical setting, pediatricians must weigh the balance of all the risks and benefits of their potential treatment. Virtually every agent in the procedural sedation armamentarium can have negative effects on a patient's cardiovascular and/or respiratory status and the physician providing sedation must be prepared to handle these potential adverse effects. Furthermore, there are a number of adverse reactions, such as nausea and vomiting, that may also result from the provision of procedural sedation. As much as pediatricians serve as the advocates for their patients to minimize pain and anxiety, they are also their patient's advocates with regard to their safety. For example, it is unlikely that procedural sedation would ever be routinely used for procedures such as venipuncture or vaccine administration [3].

In a pediatrician's practice, there are a number of indications for the provision of procedural sedation. This chapter aims to provide a framework for procedural sedation from a pediatrician's point of view, including understanding of the practice setting, the patients and the procedures themselves. This chapter is designed to apply to all sedation providers across specialties. Additionally, in trying to create an approach to procedural sedation, it is equally important to consider when the risks of the sedation outweigh the benefits which may be achieved by the procedure.

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Questions to Be Asked

Prior to the initiation of any procedural sedation, the following questions need to be considered:

1. What are the goals of the procedural sedation? Eliminating or reducing pain (analgesia)? Alleviating or reducing anxiety (anxiolysis)? Maintaining motionlessness for an imaging procedure?
2. Do I have the appropriate personnel to provide the therapy, both with regard to knowledge and experience? The proper equipment? The time to do the procedure and to monitor the patient during the recovery period?
3. Does the patient have an underlying medical condition that may complicate the provision of procedural sedation?
4. Am I prepared to handle an adverse reaction or unanticipated complication of the procedural sedation?

This chapter will attempt to provide a framework for these questions and will lay the foundation for future chapters.

Setting

First and foremost, the provision of sedation in a safe manner requires a setting that has immediately available personnel, equipment, monitoring, and protocols to manage emergency and rescue situations [5]. In particular, practitioners providing sedation must be prepared to handle the patient who has a compromise of the airway or depressed respiratory effort, both of which can result in airway obstruction, hypoventilation, hypoxemia, apnea and at worst, frank respiratory arrest. Fortunately, most severe outcomes are extremely rare. One large study found that even in centers with dedicated and specialized sedation services, one in every 200 sedations outside of the operating room required airway and ventilation intervention and one in every 400 procedures is associated with stridor, laryngospasm, wheezing or apnea [6]. While it is difficult to predict when and for whom adverse events will occur, advanced preparation may be the most critical factor in minimizing an adverse outcome [7, 8].

Personnel

Properly trained personnel are of the utmost importance in the provision of procedural sedation and there should be, at a minimum, two trained professionals present at each sedation.

The primary caregiver is the one who is responsible for providing the sedation itself. This person must be credentialed to provide sedation and should have current training in both basic (e.g., BLS) and advanced (e.g., PALS) life-support. Simple certification, however, is not enough. This primary practitioner needs to be able to recognize all potential complications of the sedation, especially the earliest signs of airway difficulties, and to manage them accordingly [9]. According to the Joint Commission, this level of competence requires not only training and education, but experience as well [10].

The secondary provider's primary responsibilities are to monitor the patient during the procedure and to inform the primary provider of any changes in the patient's cardiovascular or respiratory status. Most, if not all healthcare facilities, require that all providers be properly trained and educated as well as take part in a minimum number of sedations annually in order to ensure competence and maintain sedation privileges.

Equipment

The space where the procedural sedation takes place must have the proper equipment to minimize any adverse consequences. Table 2.1 lists the minimum equipment that must be available to provide sedation and rescue a sedated patient [5, 11].

Monitoring

A number of physiologic parameters should be monitored to ensure the safety of the patient. The

Table 2.1 Equipment required for procedural sedation

Code cart
Defibrillator Emergency airway equipment Face masks Self-inflating bag-valve-mask set-up Oro- and naso-pharyngeal airways Laryngeal mask airways (LMAs) Laryngoscope handles and blades Endotracheal tubes and stylettes
Oxygen source
May be from wall or oxygen tank, but should be able to provide positive pressure for at least 60 min or the minimum time required to be able to continuously support a patient during transfer to another medical facility or another area within the medical facility
Suction (both Yankauer-type and suction catheters for endotracheal tubes)
Vascular access equipment
Intravenous catheters Intraosseous needle Equipment to place, secure, and use the catheters (i.e., tubing, tape, arm boards, alcohol wipes, tourniquets, syringes, etc.)
Reversal agents
Naloxone or Nalmefene for opioid reversal Flumazenil for benzodiazepine reversal
Monitoring equipment
Pulse oximetry Three-lead electrocardiogram Noninvasive blood pressure monitoring End-tidal CO_2 monitoring
Means of two-way communication
Adequate lighting, electricity, and space
Medical record for documentation

Source: Data from Henderson and Womack [11] and from Cote et al. [5]

most recent guidelines from the American Academy of Pediatrics state that there should be a "functioning pulse oximeter with size-appropriate oximeter probes and other monitors as appropriate for the procedure (e.g., noninvasive blood pressure, respiratory rate, heart rate, ECG, capnography and a precordial stethoscope is encouraged in those circumstances in which the patient is not easily visible)" [5]. The American Society of Anesthesiologists updated in July, 2011 the Standards for Basic Anesthetic Monitoring. These standards specify that "during moderate or deep sedation the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs and monitoring for the presence of exhaled carbon dioxide unless precluded or invalidated by the nature of the patient, procedure or equipment" [12].

Protocols

Protocols or algorithms for how to activate back-up emergency services are essential for every setting where procedural sedation is practiced [5]. For nonhospital facilities, this includes the activation of the Emergency Medical Service (EMS) system and ambulance/transport services to the receiving hospital. It is implicit that the availability of EMS services does not obviate the practitioner's responsibility in providing initial management and rescue of the potential complications of the sedation.

There need to be written guidelines and protocols for the preprocedure assessment as well as for the monitoring of the patient during and following the procedure. Table 2.2 lists the information that should be obtained in a preprocedure

Table 2.2 Preprocedure health assessment

Age of the patient
Weight of the patient
Health history
Allergies and previous adverse drug reactions Medication history Relevant medical diseases, physical anomalies, or neurologic impairment that might increase the potential of airway obstruction Pregnancy status Relevant past hospitalizations and surgeries History of sedation or anesthesia, especially with regard to complications or adverse outcomes Relevant family history, especially with regard to anesthesia
Review of systems focusing on cardiac, pulmonary, renal, and hepatic function that might alter the patient's response to the medications used in the procedure
Vital signs
Physical examination, including a focused evaluation of the airway
Physical status evaluation (i.e., ASA classification)
Name and contact information of the patient's medical home

Source: Data from Cote et al. [5]

assessment [5]. Documentation during the procedure should be a time-based record of the monitored physiologic parameters and the timing, dosage, and effect of the administered drugs. This should start with the "time out," during which time the patient's name, procedure to be performed, and the site of the procedure are confirmed [10]. All complications, unanticipated patient reactions and ensuing treatment should be documented. Finally, there must be instructions for patients and families for care of the patient postprocedure and following discharge including contact information should there be a concern after the patient is discharged.

Patients

The practice of pediatrics is dependent on having an understanding of how patients change over time. From infancy to adolescence, children undergo tremendous physical, cognitive, and mental development. Where a patient is in his/her development will alter how we as physicians interact with our patients. An understanding of the child's cognitive development is paramount to effectively manage a patient who is about to undergo a medical procedure.

While the pain from a medical procedure may be short-lived, there is recent data to suggest that there are long-term detrimental effects on neuronal development, pain threshold and sensitivity, coping strategies, and pain perception [13]. While procedural sedation may remove the acute pain, the anxiety surrounding the procedure may actually heighten the pain experience or the patient's response to pain [13]. As such, how we prepare a patient for a medical procedure may have tremendous subsequent impact [14]. Recommendations regarding preparation for the procedure can be partitioned into timing, format, and content.

Timing refers to when one informs a patient about the procedure that is going to happen. Data suggest that information provided too far in advance of a procedure may serve to increase anxiety: children may dwell on or exaggerate the anticipated pain or forget the pertinent information completely [13]. On the other hand, inadequate time to process the information about a procedure may heighten stress. Patients undergoing a major medical procedure (e.g., surgery) will need more advanced timing as compared to something more routine, such as the administration of a vaccine. The timing will also be influenced by the developmental stage of the patient. In general, children who cannot reason or think abstractly will benefit less from early advanced information.

Format refers to how information about a procedure is conveyed. Examples of various formats include models, puppets, schematic drawings, etc. The appropriate format to be used depends greatly on one's cognitive development. For instance, young children who are at an egocentric phase of their development may not have the cognitive maturity to understand role playing with a puppet or doll.

The **content** about a procedure should relay information about the procedure itself and what the patient can expect. Accurate expectations will allow a patient to gain a sense of self-control and better cope with what is about to happen. As with timing and format, the content is greatly influenced by the developmental stage of the patient. Table 2.3 presents the sequential stages of cognitive development and the accompanying strategies to prepare a patient for a medical procedure [15].

The language we choose to explain a given procedure may also have an impact on how an upcoming procedure is perceived [16]. Dialogue that is negative, vague, or critical can increase anxiety and stress. For instance, warning that something will "hurt" or "burn" creates a negative focus. On the other hand, language that allows for distraction or provides a positive focus can attenuate anxiety and stress. For example, stating "this may feel like a pinch" or "some children say this feels warm and tingly" gives children a sensory as opposed to negative focus. Positive reinforcement such as "you are being brave" or "you did a good job of holding still" are nice ways of providing encouragement or praise. Finally, children are often very concrete thinkers. Stating that "the nurse is going to draw your blood" is too vague for most children to understand. Rather, describing the procedure in a step wise fashion (e.g., "the nurse is going to clean your arm, you will feel a cold pad to wash your skin, we will use this tourniquet to give your arm a hug, etc.") provides both sensory and detailed information that allow the children a greater sense of control [13].

Procedures

A pediatrician will encounter many different common procedures that may require procedural sedation. Depending on the procedure, a patient may require analgesia or sedation/anxiolysis or both. For instance, an infant who needs a head

Table 2.3 Childhood developmental considerations for preprocedure preparation

Age (years)	Characteristics	Strategy for preprocedure preparation
1–4	Understanding of world through sensory experiences Egocentric Trusts primary caregiver Animism Understanding > verbal ability	Use real objects to help child master the situation Reinforce good behavior Keep parent with child as much as possible
4-10	Development of reasoning Elimination of egocentrism Improved verbal communication	Allow time for questioning Provide detail Use concrete teaching materials and simple medical terms
10+	Can think abstractly Future thinking Heightened self-consciousness	Involve patient in decision-making Provide information in advance Support need for self-control and independence Offer explanations in clear, technical terms Respect privacy and self-image concerns

Source: Ferrari Lynne (Moynihan and Kurker [15]), Table 5.2, p. 71, © 1999 The Johns Hopkins University Press. Adapted with permission of the Johns Hopkins University Press

MRI will likely require a sedative agent while a cooperative adolescent may only require pain medication for a lumbar puncture. On the other hand, a child with an angulated forearm fracture will need both analgesia and sedation for the reduction. It is difficult to characterize procedures to predict the medication requirement. The temperament, cognitive development, and patient's past experience will alter what is needed for any given procedure. Table 2.4 lists the most commonly encountered procedures that may require procedural sedation. This list is not intended to be inclusive nor exhaustive. For instance, some very common procedures may require procedural sedation in a minority of patients (e.g., venipuncture). Additionally, there are some procedures on the list (e.g., endotracheal intubation, thoracentesis) that most general pediatricians will not perform once they have completed residency training.

While the choice of agents is covered in great detail in other chapters, there are a few points that bear repeating. It should be noted that while opioids do have some sedative effects, sedation often enhances analgesic efficacy. In a patient who is anxious or stressed, concomitant treatment with a sedative may reduce the needed dose of narcotic. Furthermore, the use of local and regional anesthetics (e.g., nerve blocks) may reduce the total dose of sedatives and analgesics required.

Table 2.4 Procedures that may require procedural sedation

Radiologic imaging procedures (e.g., CT scan, MRI, ultrasound)
Laceration repair
Lumbar puncture
Foreign body removal
Abscess management (e.g., incision, drainage, and packing)
Burn or wound debridement
Relocation of a dislocated joint
Fracture reduction
Joint aspiration
Prepubescent gynecologic examination
Hernia reduction
Peripherally inserted central catheter (PICC) placement
Bone marrow aspiration
Central line placement
Thoracentesis
Chest tube placement
Cardioversion
Endotracheal intubation

Other Considerations

Given the large number of resources required to safely perform procedural sedation, only primary care pediatricians in a hospital or medical center setting will likely be able to perform procedural sedation for their patients. However, this does not mean that pediatricians outside of these settings cannot assist and advise in the sedation of their patients. Our understanding of these patients and the process will allow us to play an integral role in the planning and implementation of the sedation.

As previously stated, it would be extremely unlikely that procedural sedation becomes common for, painful procedures such as phlebotomy or IV placement. Local anesthetics, however, can dramatically lessen the pain associated with procedures that require penetration of the skin [13]. In general, there are three processes by which the local anesthetic is delivered to the skin. The anesthetic can be injected locally via a small gauge needle; it can diffuse passively through the skin via a cream or gel; or be administered by a needleless system that enhances passage of the local anesthetic through the skin (e.g., heat-enhanced diffusion, iontophoresis, sonophoresis, laser-assisted passage, or pressurized gas delivery) [17]. Another topical treatment to reduce pain is the use of a vapocoolant spray. By rapidly cooling the skin, it is thought that initiation and conduction of nerve impulses are reduced and the refractoriness is increased [18]. A differentiating feature of these different methodologies is the timing and onset of anesthesia.

There have been a number of studies that have demonstrated the effectiveness of distraction as a technique to minimize pain and anxiety around painful medical procedures [13]. While there are several postulated theories as to how distraction works to reduce pain, there is much anecdotal evidence to suggest that it is an

excellent pain-management intervention. Child life therapists are another excellent resource to assist in pain management, both with regard to preparing for a procedure and providing distraction during a procedure [19]. Even proper positioning can assist in making a painful procedure less traumatic [13]. Depending on the procedure, sitting on a parent's lap or allowing a child to hold a parent's hand can help reduce procedure-related anxiety. For young infants, skin-to-skin contact, non-nutritive sucking, and sucrose water have been demonstrated to be helpful in reducing perceived pain and should be considered for certain procedures when medically allowable.

Future Directions

One of the most recent advances in our understanding of adverse reactions due to medication use lies in our increasing knowledge of pharmacogenetics. The observed differences in response between patients to the same dose of the same drug, likely is attributed to how a given individual metabolizes a given agent. For instance, differences in the level of cytochrome P-450-dependent monooxygenase activity may result in differences in both efficacy and toxicity of certain agents [20]. As an example, variants in the genotype CYP2D6 likely explain different responses to codeine, including potentially life-threatening toxicity as the result of accumulation of active metabolites of the drug [20]. In the future, our understanding of pharmacogenetics will likely be integrated into the decision-making process as we choose agents to provide procedural sedation in the safest manner possible.

In summary, it is the responsibility of the sedation provider to advocate for his/her own patients, especially with regard to pain, fear, and anxiety that may accompany a medical procedure. Being an advocate, however, does not mean that all patients should be sedated for every painful procedure. In reality, the provider must balance the pain associated with the procedure with what is safest for the patient. In essence, the approach to procedural sedation is as much choosing when not to sedate as it is to tailoring the sedation to the patient and procedure.

Case Studies

Case 1

You are in your office when a mother brings her daughter in for evaluation. She is a healthy 14-month-old with no significant past medical history who fell from a standing position and hit the back of her head on the bottom rung of the monkey bars. There was no loss of consciousness and the patient is entirely well, except for a small, 1 cm laceration in her occipital scalp. What would be your approach to managing pain for the laceration repair?

Considerations: This type of laceration in the scalp can often be repaired simply with the placement of a single staple, which can literally be done in less than a second. Given that the pain would only last for that short amount of time, it would not seem prudent to sedate the patient for this procedure.

One approach could be to use a topical anesthetic placed over 15–20 min to achieve a good deal of local anesthesia. The patient could then be held by the mother with her back to the person performing the procedure. The patient could be being read to with a picture book or watching a video at the same time to provide some distraction for this simple and quick procedure.

Case 2

You and a nurse are together seeing urgent patients for your clinic. A mother brings her 16-year-old, 90 kg son in for blood work. She

is here because the local lab where she usually goes is no longer willing to draw blood on her son. The reason is the last time he was there, he became agitated during the blood draw and knocked down the phlebotomist who tried to draw his blood. The blood work is quite urgent and needs to be done. What would your approach be to this patient?

Considerations: In general, phlebotomy is not the typical procedure for which procedural sedation is used. However, in this instance, for the safety of the patient, the person drawing the blood, and any other assistants needed to help draw the blood, it may be a good option for this patient. And while your practice may be set up to do procedural sedation and that in general, only two medical personnel are required to perform a sedation, in this instance, you may want to consider whether or not this patient needs to be referred someplace where there are more personnel available to assist with the procedure.

Case 3

Your office is in a small medical center which shares a procedure room where you can provide procedural sedation. The procedure room is well stocked, including having a pediatric code cart that is kept up-to-date. You and your nurses have done a number of procedures there and in general, you feel quite comfortable providing procedural sedation. One of your patients is brought in for evaluation of a dog bite. The patient has several deep lacerations on the face which require significant repair. Your patient's past medical history is significant for having multiple congenital anomalies. During his most recent surgery, he was noted by anesthesia to have a "difficult airway" and was hard to ventilate via bag-mask. He required fiberoptic intubation for his procedure. What would be your approach to this patient?

Considerations: The provision of procedural sedation is not simply about providing the medications, but also managing the potential complications that may occur. While this patient may tolerate sedation without any difficulty, should the patient suffer any serious adverse complication of sedation such as apnea or hypoventilation, he has already proven himself to have a "difficult airway," even in the controlled setting of an operating room. I would be reluctant to "simply sedate" this patient especially given that this may be a prolonged procedure. I think at the very least one should consult with anesthesiologist and even consider whether this procedure should take place in the operating room setting.

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Sedation Policies, Recommendations, and Guidelines Across the Specialties and Continents

3

Joseph P. Cravero

Introduction

It is the nature of pediatric sedation that the practice involves a wide variety of sedation providers and pediatric medical subspecialists. As such, there is still no consensus on "universally" applicable and acceptable guidelines. A number of guidelines, policies, and recommendations for sedation care have been promulgated by different subspecialty societies over the last 30 years. This chapter will consider some of these guidelines and put them into perspective.

The common dictionary definition of "guideline" is "general rule, principle, piece of advice." With this definition in mind, this chapter will consider several forms of guidelines – including those that come in the form of "statements," "practice advisories," "clinical policies," or "recommendations." These documents range from those that contain broad descriptions of appropriate monitoring and treatment to those that offer specific guidelines on the use of particular drugs or nil per os (NPO) intervals. While different pediatric subspecialties may have slightly different opinions and descriptions when discussing the specifics of sedation care, the common elements and considerations largely outweigh the differences.

Before beginning, it should be noted that the methodologies used to produce these guidelines vary from organization to organization. For example, the American Academy of Pediatrics (AAP) guidelines were put together by a workgroup on sedation from the Committee on Drugs [1–4]. While these guidelines were based on a careful consideration of the available literature, the exact nature of how studies were "weighted" and how conclusions were drawn is not explicitly described. The most recent guidelines of American Society of Anesthesiologists (ASA) [4] and American College of Emergency Physicians (ACEP) [5–7] are founded on an evidence-based review of pediatric sedation literature.

This chapter reviews the most recently published sedation guidelines of the various specialties in the United States and then presents the guidelines from some international societies in order to provide comparison and contrast.

American Academy of Pediatrics Guidelines

In the United States, the AAP guidelines are the most widely applied guidelines with respect to pediatric sedation. While other statements from the AAP have expanded on the importance of the

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use of sedation and analgesia for children [8–10], these guidelines still remain the standard for the AAP and have influenced the creation of safe sedation systems around the USA and internationally. Much of their lexicon and recommendations have been largely adopted by The Joint Commission in evaluating institutional compliance for safe sedation standards. The first AAP guideline for pediatric sedation was written in response to three dental deaths in 1983 (published in 1985) [1] on behalf of the American Academy of Pediatrics Section on Anesthesiology. Written in collaboration with the American Academy of Pediatric Dentistry (AAPD) and the ASA, the purpose was to develop a framework from which improved safety could be developed for children requiring sedation in order to perform a needed procedure. This initial guideline emphasized standardization on issues such as the need for informed consent, appropriate fasting prior to sedation, frequent measurement and charting of vital signs, the availability of age and size appropriate equipment, the use of physiologic monitoring, the need for basic life support (BLS) skills, and proper recovery and discharge procedures. The concept of an independent observer whose only responsibility is to monitor the patient was introduced for deeply sedated pediatric patients. Advanced airway and resuscitation skills were encouraged but not specifically required for deep sedation providers. These original guidelines defined three terms for depth of sedation: conscious sedation, deep sedation, and general anesthesia. The descriptive term "conscious sedation" was defined as "A medically controlled state of depressed consciousness that allows the protective reflexes to be maintained; retains the patient's ability to maintain a patent airway independently and continuously; and permits an appropriate response by the patient to physical stimulation or verbal command, e.g. 'open your eyes.'"

In 1992 the Committee on Drugs of the AAP revised the 1985 guideline [2]. The new iteration recognized that a patient could readily progress from one level of sedation to another and that the practitioner should be prepared to increase vigilance and monitoring as indicated. Pulse oximetry was recommended for all patients undergoing sedation. This new guideline also discouraged the practice of administering sedation at home by parents – a practice which was not infrequent in dental and radiologic sedation at that time. An addendum to the guideline was produced by the same Committee on Drugs of the AAP 2002 [11] ending the use of the term "conscious sedation" and clarifying the fact that these guidelines apply to any location where children are sedated – in or out of the hospital. The current guidelines use the terminology of "minimal sedation, moderate sedation, deep sedation, and anesthesia." These descriptions of sedation levels have been adopted by the ASA and The Joint Commission. The addendum emphasized that sedatives be administered only by those skilled in airway management and cardiopulmonary resuscitation [11].

The most current iteration of the AAP sedation guidelines was published in Pediatrics in December 2006 [3]. This set of guidelines represents a significant landmark for the field of pediatric sedation. For the first time, with the publication of this document, the Joint Commission, ASA, AAP, and the AAPD officially adopted common language to define sedation categories (minimal, moderate, deep, and anesthesia) and the expected physiologic responses for each category. The authors emphasize the concept that sedation is a continuum and that the sedation provider must be capable of rescuing a patient for a level of sedation one step deeper than that which is intended. They recommend "ongoing maintenance of critical skills for airway rescue" and reference some resources, but stop short of specific directions for how best to teach or maintain critical competencies. Deep sedation requires special expertise and personnel resources.

Credentials required to administer deep sedation [3]:

1. There must be one person available whose sole responsibility is to constantly observe the vital signs, airway patency, and adequacy of ventilation and to either administer drugs or direct their administration.
2. At least one individual, trained and competent to provide advanced pediatric life support,

airway management, and cardiopulmonary resuscitation, must be present.

This iteration of the guidelines emphasizes that as the recommendations apply to all sites where sedation is given, clear plans for rescue by Emergency Medical Systems (EMS) must be put in place for settings such as a free standing clinic or office.

The guidelines include an interesting section on drug interactions and cautions on alternative medications such at St. John's Wart, Kava, and Echinacea and their possible impact on sedation provision. The guidelines do not make any statement nor recommendation on the administration of propofol, either by anesthesiologists or nonanesthesiologists.

These guidelines distinguish monitoring requirements based on the depth of sedation as well as the setting. Pulse oximetry, heart rate, and intermittent blood pressure should be followed during moderate sedation. For deep sedation, "precordial stethoscope or capnography should be implemented for patients who are difficult to observe (i.e., MRI) to aid in monitoring adequacy of ventilation." Capnography is "encouraged" but not required, particularly in situations where other means of assessing ventilation are limited.

These guidelines make recommendations on fasting (NPO) status which continue to be followed today:

ASA/AAP NPO Guidelines

1. Clear liquids: 2 h: include water, fruit juices without pulp, carbonated beverages, clear tea, black coffee.
2. Breast milk: 4 h.
3. Infant formula, nonhuman milk.
4. Light meal and solid food: 6 h.

Recovery criteria and considerations are also enumerated, including a suggestion for the use of (new) simple "wakefulness" measures as part of the discharge criteria (where a child is simply observed for his/her ability to remain awake for a specified period of time (15–20 min) prior to discharge) [3].

American Society of Anesthesiologists (ASA) Policies and Recommendations

While the ASA has not produced a document specific for pediatric sedation, issues relating to pediatric patients are mentioned in almost all of the sedation-related publications it has produced. The ASA has many statements and guidelines that address sedation by nonanesthesia providers including *Practice Guidelines for Sedation and Analgesia by Nonanesthesiologists* [4]. *Continuum of Depth of Sedation – Definition of General Anesthesia and Levels of Sedation/Analgesia; Statement on Granting Privileges for Administration of Moderate Sedation to Practitioners who are not Anesthesia Professionals; Practice Guidelines for Preoperative fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures; Statement on Safe Use of Propofol; and Statement on Granting Privileges to Nonanesthesiologist Practitioners for Personally Administering Deep Sedation or Supervising Deep Sedation by Individuals Who are not Anesthesia Professionals.* (All statements and other documents are available at: http://www.asahq.org/publicationsAndServices/sgstoc.htm.)

The Sedation Practice Guidelines for Practitioners who are not Anesthesiologists [4] is probably the most widely quoted document concerning sedation that the ASA has produced. The latest iteration of this document was published in 2002 as an update/revision of the original 1995 guidelines [4, 12]. The stated purpose of the guideline is to "allow clinicians to provide their patients with the benefits of sedation/analgesia while minimizing the associated risks." These guidelines were developed by a task force using an evidence-based "strength of the evidence" methodology.

The ASA guidelines are consistent with the AAP in many respects. They describe the sedation levels identical to the AAP and The Joint Commission guidelines. They require that the sedation provider be able to rescue patients from a level deeper than intended. The authors also apply the current ASA recommendations on NPO times

(2 h for clear fluids, 4 h for breast milk, 6 h for light meals and formula, 8 h for full meals) to elective sedation. The ASA guidelines are similar to those of AAP in their recommendation for ECG, blood pressure, and pulse oximetry for all deep sedation patients. Continual monitoring of sedation depth through stimulation/response analysis is recommended. Until 2011, the ASA emphasized but did not require capnography, stating that capnography should be considered, but is not required, for all patients receiving deep sedation and for patients whose ventilation cannot be directly observed during moderate sedation. The American Society of Anesthesiologists updated in July, 2011 the Standards for Basic Anesthetic Monitoring. These standards specify that "during moderate or deep sedation the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs and monitoring for the presence of exhaled carbon dioxide unless precluded or invalidated by the nature of the patient, procedure or equipment." This updated ASA standard is landmark- the first time that end-tidal carbon dioxide monitoring has been made a standard of care for moderate as well as deep sedation [13].

In 2005 the ASA produced the "Statement on granting privileges for administration of moderate sedation to practitioners who are not anesthesia professionals." This is a detailed statement that defines the different groups/qualifications of sedation providers: The Anesthesia Professional (anesthesiologist, Certified Registered Nurse Anesthetist (CRNA), Anesthesiologist Assistant (AA), Nonanesthesiologist Sedation Practitioner (other physicians, dentists, podiatrists), Supervised Sedation Professional (licensed registered nurse, advanced practice nurse, etc.)). This grouping has raised some controversy, as the term "nonanesthesiologist" can represent physicians of various levels of skill, training, and experience [14].

The ASA defines the rescue capabilities that are required for sedation providers at each level of sedation. In 2006 they deviated from the AAP in that they restricted the administration of deep sedation to those of particular qualifications: To practitioners who are qualified to administer general anesthesia or to appropriately supervise anesthesia professionals (http://www.asahq.org/For-Healthcare-Professionals/Standards-Guidelines-and-Statements.aspx). This individual should have no other responsibilities except to deliver sedation and monitor the patient throughout. This "Statement on granting privileges to non-anesthesiologist practitioners for personally administering deep sedation or supervising deep sedation by individuals who are not anesthesia professionals" was supplanted on October 20, 2010 by the ASA Statement on Granting Privileges for Deep Sedation to Non-Anesthesiologist Sedation Practitioners [15]. It recommends that the nonanesthesiologist be able to bag-valve-mask ventilate, insert an oro/pharyngeal airway and laryngeal mask airway, and perform an endotracheal intubation. Training should include a minimum of 35 patients, inclusive of simulator experience. Practitioners should be familiar with the use and interpretation of capnography. Deep sedation of children requires PALS and ACLS certification as well as separate education training and credentialing. The ASA recognizes the Center for Medicare and Medicaid Services (CMS) as defining those qualified to administer deep sedation. The Hospital Anesthesia Services Condition of Participation 42 CFR 482.52 (a) of 2010 [16] limits deep sedation to be delivered only by an anesthesiologist, nonanesthesiologist MD or DO, dentist, oral surgeon, podiatrist, CRNA, or Anesthesia Assistant (AA) [16, 17].

These CMS guidelines toward nonanesthesia providers of sedation were revised in January 2011 in the PUB 100–07 State Operations Provider Certification which revises Appendix A for various provisions of 42 CFR 482.52 concerning anesthesia services. These revisions were made in response to feedback from practitioners. Important changes in these guidelines stem from the CMS acknowledgement that the individual hospitals may establish their own policies and procedures with respect to the qualifications of analgesia providers and the clinical situations which distinguish anesthesia from analgesia. The policies must follow nationally recognized guidelines and can include guidelines of one or more specialty societies.

The ASA "Statement on the Safe Use of Propofol" first published in 2004 and amended in 2009, advises that "the involvement of an anesthesiologist in the care of every patient undergoing anesthesia is optimal. However, when this is not possible, non-anesthesia personnel who administer propofol should be qualified to rescue patients whose level of sedation becomes deeper than initially intended and who enter, if briefly, a state of general anesthesia [18]."

The distinction between sedation, deep sedation, and Monitored Anesthesia Care (MAC) is frequently misunderstood. To clarify these definitions, the ASA in 2009 amended the document entitled: Distinguishing "MAC" from Moderate Sedation/Analgesia (Conscious Sedation) to differentiate between the two levels of care. Important distinctions were that MAC entails an anesthesia assessment and the delivery of sedation by a provider who is prepared and qualified to assess and manage physiological or medical issues and to convert to a general anesthetic. In general, those who administer moderate sedation would not expect to progress to a condition in which the patient could not maintain his own airway [19].

The Joint Commission: Where We Stand Now

Issues relating to sedation (in general) and pediatric sedation in specific are found in a variety of locations in the *The Joint Commission Handbook* and website (www.jointcommission.org). The JCAHO 2004 Comprehensive Accreditation Manual for Hospitals was intended to set the standards for sedation and anesthesia care for patients in any setting [20].

The Joint Commission recommendations are important when considering the credentialing and privileging of sedation providers. The Joint Commission requires that hospitals define the scope of practice for practitioners. It is important to distinguish the term "credentialing" from "privileging." "Credentialing" is the process whereby designated hospital appointees assure that physicians who work in the hospital have the appropriate education, training, and licensure to practice in the institution. "Privileging" specifically gives permission to hospital staff to provide care in various clinical settings or perform particular procedures in a given institution. With regard to sedation privileging, each healthcare facility is mandated by The Joint Commission to approve a plan to provide sedation and anesthesia care. Each institution must outline the criteria for determining which practitioners are qualified to provide the service.

It is important to recognize the evolution of the role of the Anesthesiology Department in the delivery of sedation as outlined by The Joint Commission. Earlier Joint Commission publications placed responsibility for sedation oversight on the Department of Anesthesiology and its Chairman [19]. Subsequent revisions of this document have revised the language: The Anesthesiology Department plays an important advisory role but is not directly responsible for sedation care, privileging, or quality assurance.

In the current 2007 Joint Commission manual, there are recommendations for the training that may be provided for other sedation providers: "Individuals administering moderate or deep sedation and anesthesia are qualified and have the appropriate credentials to manage patients at whatever level of sedation or anesthesia is achieved, either intentionally or unintentionally [21]." Referring specifically to deep sedation it states, "individuals must be qualified to rescue patients from general anesthesia and are competent to manage an unstable cardiovascular system as well as a compromised airway and inadequate oxygenation and ventilation [21]." It goes on to specify "Each organization is free to define how it will determine that the individuals are able to perform the required types of rescue. Acceptable examples include, but are not limited to, ACLS certification, a satisfactory score on a written examination developed in concert with the department of anesthesiology, a mock rescue exercise evaluated by an anesthesiologist [21]."

Although the Joint Commission still believes that Anesthesiology Departments should play a role in the development of training and privileging programs for sedation, they no longer hold the central role of being "in charge" of sedation

services. Key roles in sedation oversight may be filled by qualified specialists of many different subspecialties.

American College of Emergency Physicians Guidelines

The American College of Emergency Medicine (ACEP [7]) has put forward a wide range of statements, clinical practice advisories, and clinical policy statements concerning sedation. The 2008 ACEP Policy Compendium includes an important statement *Procedural Sedation in the Emergency Department* (www.acep.org/practres.aspx?id=29644). This statement begins with a strongly worded sentence: "Emergency physicians and nurses under their supervision are qualified to provide procedural sedation/analgesia in the emergency department, and ACEP is the authoritative body for the establishment of guidelines for procedural sedation and analgesia (PSA) by emergency physicians."

In 1998 and 2005 the ACEP produced *Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department* [7]. Similar to the ASA guidelines, the ACEP guidelines apply to all patients, adults, and children who receive sedation. They recognize that sedation is a continuum and maintain that practitioners should possess competence in cardiovascular resuscitation and airway management which should include a patient who has achieved general anesthesia. The ACEP considers these skills, including the administration of propofol and deep sedation, to be a fundamental part of the emergency medicine training curriculum and inclusive of the training required of all board-certified emergency physicians [7, 22].

The ACEP guidelines deviate from those of the AAP and ASA with respect to NPO guidelines. Both the AAP and ASA recommend fasting intervals for elective cases similar to those required for general anesthesia – specifically 2 h for clear liquids, 4 h for breast milk, 6 h for formula, and 8 h for full meals. These guidelines do not make recommendations for the non-elective sedation case. The ASA and ACEP differ in their consideration of NPO status in emergent situations. The ASA guidelines state "Patients undergoing sedation/analgesia for elective procedures should not drink fluids or eat solid foods for a sufficient period of time to allow for gastric emptying before their procedure. In urgent, emergent, or other situations in which gastric emptying is impaired, the potential for pulmonary aspiration of gastric contents must be considered in determining (1) the target level of sedation, (2) whether the procedure should be delayed, or (3) whether the trachea should be protected by intubation." The AAP guidelines are a bit less specific stating only "for emergency procedures the risks of sedation and the possibility of aspiration must be weighed against the benefits of performing the procedure promptly."

By the very nature of their work, emergency medicine sedation providers must cope with patients who do not meet approprite NPO criteria and are not having "elective" procedures. In the last 10 years, there have been several studies in the emergency medicine literature that have reported very low rates of aspiration or pulmonary complications in patients who were sedated without meeting the NPO recommendations from the AAP or ASA [23, 24]. Previous publications from the ACEP have concluded that there is insufficient evidence to conclude that fasting actually changes outcome for sedation (see above) [25].

In 2006, the ACEP produced a document on fasting prior to sedation [26]. This clinical practice advisory is titled "Fasting and Emergency Department Procedural Sedation and Analgesia: A Consensus-Based Clinical Practice Advisory." The paper begins with an extensive review of the guidelines that have been set forth by the ACEP, AAP, and ASA concerning NPO status, and considers them in the context of the Emergency Department setting. This consensus-based clinical advisory concludes that there is actually scarce literature to document the perceived risk that various NPO times pose with respect to sedation complications. The authors suggest that the issue of NPO interval needs to be considered in the context of the urgency and duration of the procedure as well as the risk stratefication of the patient, nature of food intake, and depth/type of sedation targeted. The result is a somewhat complex strategy

Standard-risk patient[a]

Oral intake in the prior 3 hours	Procedural Urgency[b]			
	Emergent Procedure	*Urgent Procedure*	*Semi-Urgent*	*Non-Urgent*
Nothing	All levels of sedation	All levels of sedation	All levels of sedation	All levels of sedation
Clear liquids only	All levels of sedation	All levels of sedation	Up to and including brief deep sedation	Up to and including extended moderate sedation
Light snack	All levels of sedation	Up to and including brief deep sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only
Heavier snack or meal	All levels of sedation	Up to and including extended moderate sedation	Minimal sedation only	Minimal sedation only

Higher-risk patient[a]

Oral intake in the prior 3 hours	Procedural Urgency[b]			
	Emergent Procedure	*Urgent Procedure*	*Semi-Urgent*	*Non-Urgent*
Nothing	All levels of sedation	All levels of sedation	All levels of sedation	All levels of sedation
Clear liquids only	All levels of sedation	Up to and including brief deep sedation	Up to and including extended moderate sedation	Minimal sedation only
Light snack	All levels of sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only	Minimal sedation only
Heavier snack or meal	All levels of sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only	Minimal sedation only

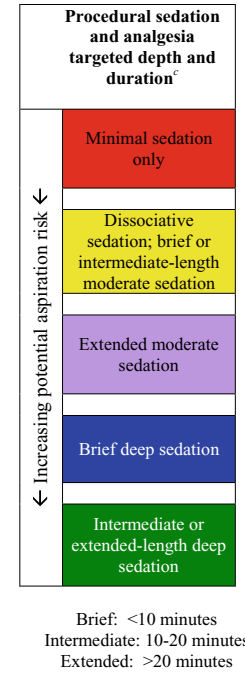

Figure. Prudent limits of targeted depth and length of ED procedural sedation and analgesia according to presedation assessment of aspiration risk

Fig. 3.1 ACEP NPO considerations and aspiration risk. (Adapted from Green et al. [26], Reprinted with permission from Elsevier)

that weighs NPO time vs. Emergent/Urgent/Semiurgent nature of the case vs. duration of the procedure. Figure 3.1 schematically describes the recommendations that result from these guidelines [26]. Important however, is their guidelines for non-elective sedation of patients who are not considered NPO by ASA or AAP standards. The guidelines state that although "recent food intake is not a contraindication for administering Procedural Sedation and Analgesia (PSA), the emergency physician must weigh the risk of pulmonary aspiration and the benefits of providing PSA in accordance with the needs of each individual patient [7]." The NPO recommendations state that "recent food intake is not a contraindication for administering PSA, but should be considered in choosing the timing and target level of sedation [7, 26]."

In 2004 and 2008, the ACEP published evidence-based guidelines on the use of specific medications for use in pediatric sedation: *Clinical policy: evidence-based approach to pharmacologic agents used in pediatric sedation and analgesia in the emergency department*; [5] and *Clinical policy: Critical issues in the sedation of pediatric patients in the emergency department* [25]. The "Critical Issues" statement supported earlier recommendations on NPO status and reviewed the use of sedatives which included nitrous oxide, chloral hydrate, and sucrose. Important statements include "Procedural sedation may be safely administered to pediatric patients in the ED who have had recent oral intake [25]."

Other ACEP publications include a clinical practice advisory on Propofol use in the Emergency Department [22], and a clinical practice guideline on ketamine use in the Emergency Department [6]. Both of these documents support the use of these drugs for sedation in the Emergency Department, expanding on the evidence-based guideline recommendations from the Clinical Policy on pharmacological agents mentioned above [5]. The ACEP recommendations

for physiological monitoring deviate from the ASA and AAP with respect to pulse oximetry application: Pulse oximetry is not mandatory. The guidelines advise that pulse oximetry may not be necessary when the patient's level of consciousness is minimally depressed and verbal communication can be continually monitored. Pulse oximetry is recommended, however, when there is an increased risk of developing hypoxemia, such as when high doses of drugs or multiple drugs are used, or when treating patients with significant comorbidity. Capnography, although not required, is acknowledged by ACEP to be a monitor which may allow more rapid identification of hypoventilation than pulse oximetry alone [27].

American Dental Association Sedation Guidelines

The American Dental Association (ADA) guidelines regarding sedation are posted on their website at www.ada.org/sections/professionalResources/pdfs/anesthesia_guidelines.pdf. The guidelines acknowledge the depths of sedation consistent with that described by the AAP and the ASA. It contains descriptions of routes of administration for sedative medications, ASA classification for sedation patients, and monitoring guidelines for sedated patients. There is a very specific outline of the training required for dentists regarding various levels of sedation, including specific educational programs and life support training. In this regard the guidelines are more detailed than those provided by other organizations. Deep sedation requires the presence of a minimum of three individuals: one dentist who is credentialed to administer deep sedation or anesthesia and two additional personnel who have current certification of successfully completing a BLS Course for the Healthcare Provider. There are two requirements to qualify for deep sedation certification: Completion of an advanced education program on the administration and management of deep sedation or anesthesia, which must be accredited by the ADA Commission on Dental Accreditation, and a current certification in both BLS for Healthcare Providers and Advanced Cardiac Life Support (ACLS) or an appropriate dental sedation/anesthesia emergency management course. The dentist administering deep sedation or general anesthesia must remain within the facility until the patient meets discharge criteria (or is discharged) and must monitor the patient continuously until the patient meets the criteria for recovery. Those who provide pediatric sedation must have Pediatric Advanced Life Support (PALS) in addition to directed pediatric training and education [28, 29].

The guidelines are presented in sections, each of which iterates a sedation level: Minimal, Moderate, and Deep Sedation sections. Specific recommendations are given for training of sedation providers, preoperative preparation of patients, monitoring and documentation, recover and discharge criteria, and personnel/equipment requirements. The document is intended for adults and for children 12 years of age and below. The ADA refers to the AAP/AAPD *Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures* and *Use of Deep Sedation and General Anesthesia in the Pediatric Dental Office* [3, 30]. These guidelines address some issues unique to the office-based dental practice and to the special needs child. If the dental patient undergoing deep sedation or general anesthesia is mentally and/or physically challenged, it may not be possible to have a comprehensive physical examination or appropriate laboratory tests prior to administering care. In these situations, the dentist responsible for administering the deep sedation or general anesthesia should document the reasons preventing the recommended preoperative assessment prior to administering sedation [3]. Nitrous oxide is a recognized and acceptable sedative, alone or in combination with other sedatives [3].

American Society of Gastroenterologists

The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy has recently published guidelines for deep sedation, the administration of propofol by nonanesthesiologists and pediatric sedation for

gastrointestinal procedures and endoscopy [31]. All of these guidelines were written after a review of the MEDLINE and PubMed database. The recommendations are rated "A," "B," or "C" based on the weight of the evidence available. A level identifies statements supported by prospective randomized trials and C level identifies expert opinion in the absence of peer-reviewed evidence. The chronological history leading up to these 2009 guidelines will be detailed below [31, 32].

The first guideline was published in 2002 and entitled *Guidelines for the Use of Deep Sedation and Anesthesia for GI Endoscopy* [32]. This guideline reviews the levels of sedation and the importance of presedation assessment in order to customize sedation for the needs of the patient. Planning is identified as particularly important for those with specific emotional issues, drug use history, and those who are undergoing extensive procedures. There are no specific references to, or recommendations for, the pediatric population.

Pharmacologic agents are reviewed and include guidelines for the indications and use of droperidol (in addition to midazolam and fentanyl). This guideline is unique in its recommendation for droperidol as a third drug if needed. There is an accompanying warning about cardiac issues related to droperidol and the need for extended ECG monitoring when it is utilized.

The majority of this guideline is devoted to the role of propofol and the relative risks vs. benefits of its use in endoscopy. Personnel preparation and monitoring requirements for propofol sedation are carefully delineated [32]:

1. At least one person who is qualified in both basic and advanced life support skills (i.e., tracheal intubation, defibrillation, use of resuscitation medications).
2. Physiologic monitoring should include pulse oximetry, electrocardiography, and automated blood pressure measurement. Monitoring oxygenation by pulse oximetry is not a substitute for monitoring ventilatory function.
3. Equipment for airway management and resuscitation.
4. Trained personnel dedicated to the continuous and uninterrupted monitoring of the patient's physiologic parameters and administration of propofol.
5. Extended monitoring with capnography should be considered as it may decrease the risks during deep sedation.

Published in 2002, this guideline concludes that although propofol does not appear to offer a significant advantage over standard benzodiazepine/opiate techniques for routine endoscopy procedure, it does confer significant advantages for longer and more complicated procedures (Level "A" recommendation). The authors also discuss the provision of propofol sedation by nonanesthesiologists including other physicians and registered nurses. Anesthesiology assistance is recommended for specific situations including prolonged or therapeutic endoscopic procedure requiring deep sedation, anticipated intolerance to standard sedatives, increased risk for complication because of severe comorbidity (ASA class III or greater), and increased risk for airway obstruction because of anatomic variant. These final recommendations are included at a "C" level.

A second publication entitled *Guidelines for Conscious Sedation and Monitoring During Gastrointestinal Endoscopy* was published in 2003 in the journal Gastrointestinal Endoscopy [33]. They refer to "conscious sedation" as a level of equivalence to "moderate sedation." These guidelines review the data on endoscopy-related complications – noting that over 50% of complications are related to cardiopulmonary side effects with the majority relating to aspiration, oversedation, hypoventilation, vasovagal episodes, and airway obstruction. They note that the risk of cardiovascular complications is dependent on the patient's underlying medical condition and the procedure to be performed – The combination of high-risk patients and high-risk procedures represent the highest risk.

These guidelines support the monitoring recommendations of the ASA and AAP: Required monitoring during sedation for endoscopy includes recording of the heart rate, blood pressure, respiratory rate, and oxygen saturation. Capnography is advised for prolonged cases but not required.

Several drugs are mentioned for conscious sedation during endoscopy. Benzodiazepines and opiates (along with reversal agents) are mentioned in detail along with droperidol and promethazine. Unique to this set of guidelines, "pharyngeal" anesthesia is reviewed. Specific mention is made of the risk of methemoglobinemia with benzocaine administration. In reference to deep sedation, the authors suggest that propofol is superior to standard benzodiazepine/opiate sedation for complex procedures and acknowledge that its use in routine upper and lower endoscopic procedures is controversial with little proven benefit over standard moderate sedation [33].

The most recent and pertinent publication regarding sedation specifically for pediatric endoscopy was published in 2008 as *Modifications in Endoscopic Practice for Pediatric Patients* [34]. This document addresses many issues relating to sedation in children and for pediatric endoscopy. For example, the authors review indications and contraindications for endoscopy in children, the appropriateness of pediatric vs. adult endoscopists for various procedures in children, and the appropriate preparation of patients for these studies. They include discussions of the proper equipment to use for pediatric endoscopy and the indications for antibiotic prophylaxis.

Important cautions are that airway obstruction is more common in children and because of higher oxygen consumption, it can lead to the rapid onset of hypoxia in the face of apnea (and therefore recommend the routine use of oxygen during endoscopic sedation in this age group). The authors note that general anesthesia is often used for pediatric endoscopy and that the number of centers using propofol sedation or general anesthesia for endoscopy appears to be increasing [34, 35]. One study from 1995 cites equivalent safety and efficacy when using a standardized procedural sedation protocol (opiate plus benzodiazepine) when compared to general (potent inhalation) anesthesia [36]. The authors also note that when propofol sedation is compared to "general anesthesia," it has been found to result in less total time for sedation/anesthesia and equal safety [37].

In 2009, the American Society of Gastroenterologists published their position statement for nonanesthesiologist administration of propofol for GI endoscopy [31]. The guidelines state that clinically important benefits of propofol in average-risk patients undergoing upper endoscopy and colonoscopy have not been consistently demonstrated with regard to patient satisfaction and safety. It supports that propofol can be safely and effectively given by nonanesthesiologist physicians and nurses provided they have undergone appropriate training and credentialing in administration and rescue from potential pulmonary and cardiovascular complications. The summary section makes specific recommendations for sedation for pediatric endoscopy. They generally follow AAP and ASA standards [31]:

1. All pediatric patients should receive routine oxygen administration and should be monitored with a minimum of pulse oximetry and heart rate monitoring.
2. In deeply sedated patients one individual having no other responsibilities should be assigned to monitor the patient's cardiac and respiratory status and to record vital signs.
3. The presence of personnel trained specifically in pediatric life support and airway management during procedures requiring sedation is strongly recommended.

The Debate: Granting Privileges for Sedation to Non-Anesthesiologists

An ongoing area of debate revolves around the credentialing and privileging of non-anesthesiologists to administer sedation. In October 2010, the ASA issued a Statement on Granting Privileges for Deep Sedation to Non-Anesthesiologist Sedation Practitioners [15]. The ASA Statement recommends that non-anesthesiologists be proficient in advanced airway management for rescue when they deliver deep sedation. This proficiency and competency would be determined by the Director of Anesthesia Services of the facility in which the sedation is delivered [15]. In addition, the ASA specified that performance evaluation and a performance improvement program would be required for privileging- both of which would be developed

with and reviewed by the Director of Anesthesia Services [15].

In response to the above ASA Statement, in July 2011 the American College of Emergency Physicians released a policy statement entitled Procedural Sedation and Analgesia in the Emergency Department (ED): Recommendations for Physician Credentialing, Privileging, and Practice [38]. This Policy iterated that the chief of the emergency medicine service at each institution will be responsible for establishing criteria for credentialing and recommending emergency physicians for sedation privileges. Sedation training should "focus on the unique ED environment". Furthermore, the capability of qualified ED nurses to administer propofol, ketamine, and other sedatives under the direct supervision of a privileged emergency physician is condoned. The Policy acknowledges that deep sedation may be accomplished with the ED physician both administering sedation and performing the procedure.

The training, credentialing and privileging process and requirements for non-anesthesia specialists will likely remain an area of ongoing debate. Regardless, the introduction and implementation of structured sedation training, regardless of the specialty which initiates and is responsible for the training program, will only serve to benefit the practice and delivery of sedation.

International Guidelines

A wide variety of sedation guidelines specific to pediatrics or with application to pediatrics have been published by various specialty societies and international organizations. Some are largely consistent with the recommendations of the AAP, others are not. It is not possible to review and highlight all of the similarities and differences between the existing sedation guidelines worldwide. Chapters 14, 17, and 18 detail the most recent sedation guidelines published by the National Institute of Health (NICE) in the United Kingdom (2011) [39], the Dutch Institute of Healthcare Improvement in the Netherlands (2011) [40], the Endoscopy Section of the German Society for Digestive and Metabolic Diseases (2009) [41], and the adult and pediatric guidelines of the South African Society of Anesthesiologists (2010 and 2011) [42, 43]. A sample of sedation statements and guidelines published worldwide include the following:

1. Scottish Intercollegiate Guidelines Network [44].
2. Australasian College for Emergency Medicine, Australian and New Zealand College of Anaesthetists [45].
3. Canadian Consensus Guidelines. Canadian Association of Emergency Physicians [46].
4. British Society of Gastroenterology [47].
5. Standing Dental Advisory Committee – UK [48].
6. NeuroAnesthsia and Neruointensive Study Group of the Italian Society of Anesthesia [49].
7. Standing Dental Advisory Committee, Department of Health – UK. *Conscious Sedation in the Provision of Dental Care. Report of an Expert Group on Sedation for Dentistry 2003*. Available at: www.dh.gov.uk/PublicationsandstatisticsPublications. Accessed 2 Jan 2008.
8. The Working Group on Endoscopy, Austrian Society of Gastroenterology and Hepatology [50].
9. South African Society of Anaesthesiologists (SASA) Sedation Guidelines [43].
10. South African Society of Anaesthesiologists (SASA) Paediatric Procedural Sedation and Analgesia (PSA) Guidelines [42].
11. National Institute for Health and Clinical Excellence. Sedation for diagnostic and therapeutic procedures in children and young people (Clinical guideline 112) 2010 [39] (http://guidance.nice.org.uk/cg112).
12. Sedation Guidelines for Gastrointestinal Endoscopy 2008 of German Society for Digestive and Metabolic Diseases [41].
13. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anesthesiology Guideline: Non-Anesthesiologist Administration of Propofol for G1 Endoscopy [51].
14. Dutch Institute for Healthcare Improvement (CBO), Pediatric Guidelines for Sedation

and/or Analgesia (PSA) at Locations Outside the Operating Theatre from the Netherlands Society of Anesthesiologists and the Dutch Society of Pediatrics [40].

Even within Europe, there is a lack of consensus and agreement between the guidelines, particularly with respect to pediatrics, deep sedation, and propofol. One example of this is the sedation guidelines of Scotland. The Scottish National Guidelines of 2004 were written only for minimal and moderate sedation, as anything beyond (deep sedation included) requires an anesthesiologist and is treated as a general anesthetic [44]. Propofol is limited to anesthesiologist administration only. Scotland offers a unique acknowledgement on the role of the child and parent in the sedation process. In 1995, the Child Scotland Act specified that an informed consent be obtained from the child when appropriate. The presence of the parents is recommended during the sedation, in hopes of providing emotional support [52].

Summary

The practice of sedation for children has advanced considerably over the last 40 years. Sedation guidelines have evolved, with new editions, updates, and addendums in order to reflect the change in practice and the published literature. As outlined in this chapter, there are a large number of guidelines that address pediatric sedation. There is a general lack of consensus on NPO status for sedation and on whether nonanesthesiologists should administer deep sedation or propofol. In general, however, all of the guidelines are congruent with regard to the need for patient assessment and preparation and for appropriate competency-based training and credentialing for sedation providers. Future efforts should be aimed at designing clinical studies with defined endpoints and outcomes. Worldwide participation in these studies, involving all specialties, will establish safety data which could direct the creation of more unified sedation guidelines. Particularly with children, unified recommendations from the AAP, ASA, AAPD, ADA, The Joint Commission, ACEP, and American Society of Gastroenterologist together with a consensus among the different specialties worldwide, would offer a landmark first step in the advancement of pediatric sedation.

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4 Sedation Scales and Discharge Criteria: How Do They Differ? Which One to Choose? Do They Really Apply to Sedation?

Dean B. Andropoulos

Introduction

Assessing the depth of sedation in children is critically important to determine whether the goals of sedation are met without exposing the patient to the risk of adverse outcomes. In a clinical model of pediatric sedation [1], the patient's state can range from fully awake undergoing a painful procedure without sedation or analgesia to apnea, hypoxia, and death from oversedation (Fig. 4.1). Clearly, having the sedated child's state in the goal zone is important, and objective tools to assess sedation depth are necessary to standardize depth of sedation. Additionally, having objective assessment scales available to rate a child's readiness for discharge from a sedation recovery area is also important, as premature discharge may lead to adverse events and even death [2–4]. This chapter will review commonly used pediatric sedation scales, focusing on procedural sedation. Then methods of sedation assessment using processed EEG will be reviewed and compared to pediatric sedation scales. Finally, commonly used scales to assess recovery from sedation and readiness for discharge from sedation will be discussed.

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Sedation Scales

The Joint Commission, American Academy of Pediatrics, and the American Society of Anesthesiologists have recently revised their definitions of the levels of pediatric sedation [5, 6] (Table 4.1, Fig. 4.2). The four levels of sedation are now minimal, moderate, deep, and general anesthesia. The previously used term "conscious sedation" has been eliminated because it was misleading, and inapplicable particularly in pediatric patients who can change rapidly from minimal to deep levels of sedation. Any assessment of levels of sedation needs to take these basic considerations into account.

Sedation scales are indeed necessary for pediatric procedural sedation, particularly when practiced by nonanesthesiologists. For example, Reeves et al. [7] studied 16 children undergoing propofol sedation for bone marrow aspiration by nonanesthesiologists, and found that for all children, their level of consciousness, motor activity score, and bispectral index score was consistent with either deep sedation or general anesthesia at some point during the procedure. In a large pediatric procedural cohort, Cravero et al. assessed 49,836 propofol sedations. Complications were noted in 5.92% of patients, including an airway or pulmonary complication in 1.17%, yet there was no assessment of depth of sedation reported [8]. Sedation scales are essential to minimize complications from sedation. They can provide early warning of sedation that is

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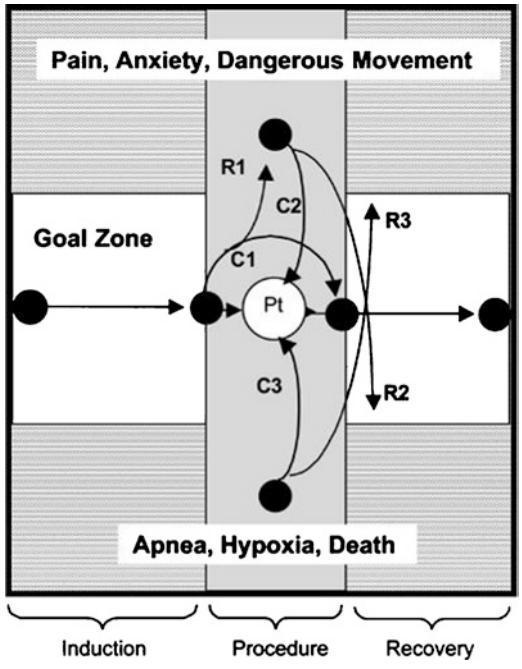

Fig. 4.1 A working model of pediatric sedation. The *x*-axis is the time of phase of sedation. The *y*-axis is the depth of sedation, ranging from inadequate to oversedation. A sedation scale should be able to accurately assess the depth of sedation and maximize the chance that the patient is in the goal zone. The *black dots* are the patient at a single point in time, ranging from preprocedure, through intra and postprocedure. (**c**) designates the work done by the provider to counteract the adverse effects of sedation or accomplish a task. C1 is the procedure control loop, C2 the procedural pain and anxiety control loop, and C3 the sedation-related respiratory depression control loop. R1 is the undesired side effects of therapeutic action: R1 undersedation and pain; R2 oversedation, and R3 rescue from oversedation. (From Cravero et al. [1], reprinted with permission from Wolters Kluwer Health)

Table 4.1 American Academy of Pediatrics/Joint Commission/American Society of Anesthesiologists Definitions of Levels of Sedation

Minimal sedation (anxiolysis): A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected
Moderate sedation (previously called conscious sedation or sedation/analgesia): A drug-induced depression of consciousness during which patients respond purposefully to verbal commands either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained
Deep sedation: A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation (*note*: reflex withdrawal from a painful stimulus is not considered a purposeful response). The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained
General anesthesia: A drug-induced loss of consciousness during which patients are not arousable, even to painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired

Source: Data from American Society of Anesthesiologists. ASA Standards, Guidelines and Statements, October 2007. Available at www2.asahq.org/publications/p-106-asa-standards-guidelines-and-statements.aspx

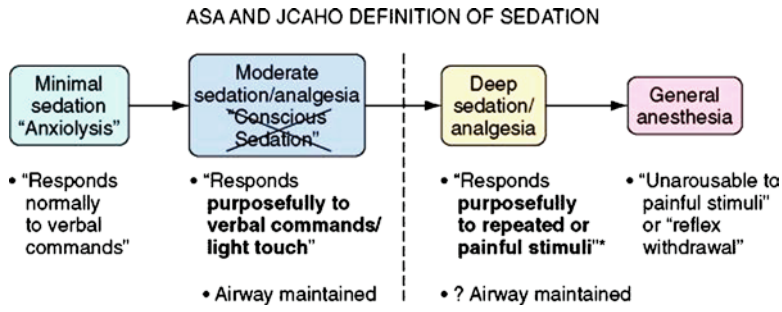

Fig. 4.2 The sedation continuum. A patient may readily pass from a light level of sedation to deep sedation or general anesthesia. Healthcare providers must be prepared to increase vigilance and intensity of monitoring consistent with the depth of sedation. One should consider all children younger than the age of 6 years as deeply sedated because "conscious sedation" in this age group for most children is an oxymoron. (*ASA, American Society of Anesthesiologists; JCAHO, Joint Commission on Accreditation of Healthcare Organizations*.) (Reproduced and used with permission from Kaplan et al. [6])

deeper than intended and allow the practitioner to intervene proactively, instead of having to rescue the patient from an episode of hypoxemia from airway obstruction or apnea. The ideal sedation scale would be applicable to children of all ages, easy and rapid to administer to allow repeated objective assessment, and correlate both with depth of sedation necessary for successful completion of the procedure and with adverse effects of sedation, i.e., airway obstruction, hypoxemia, hypotension, and bradycardia. It would be validated against other accepted scales, and also an objective method of assessment such as a processed EEG technique. And, it would be further validated in very large numbers of patients to determine whether the scale correlates with outcomes. Unfortunately, no such ideal sedation scale exists. However, there are a number of objective and semiobjective methods, some validated, to assess depth of sedation. This chapter will review the currently available and utilized sedation scales and assessment methods.

The Ramsay Scale

The Ramsay Sedation Scale (RSS) was described by Ramsay and colleagues in 1974 for the purpose of monitoring sedation with alphaxalone/alphadolone [9] (Table 4.2). It has been validated by several methods including a modified Glasgow Coma Scale and the Sedation Agitation Scale [10]. The Ramsay scale was one of the earliest sedation scales, and although not strictly validated in children, it is one of the most widely used scales for assessing and monitoring pediatric sedation in daily practice, as well as in clinical research. RSS spans the continuum of sedation but does not clearly separate purposeful from nonpurposeful responses.

Table 4.2 Ramsay Scale

Level	Characteristics
1	Patient awake, anxious, agitated, or restless
2	Patient awake, cooperative, orientated, and tranquil
3	Patient drowsy, with response to commands
4	Patient asleep, brisk response to glabella tap or loud auditory stimulus
5	Patient asleep, sluggish response to stimulus
6	Patient has no response to firm nail-bed pressure or other noxious stimuli

Source: Data from Ramsay et al. [9]

A later modification of the Ramsey scale more clearly coincides with the AAP and Joint Commission guidelines (Table 4.3) [6]. A score of 2–3 is anxiolysis, 4–5 is moderate sedation, 6 is deep sedation, and 7–8 is general anesthesia.

The Observer's Assessment of Alertness/Sedation Scale and Modified Observer's Assessment of Alertness/Sedation Scale

The Observer's Assessment of Alertness/Sedation scale (OAA/S) [11] was developed to measure the alertness of adult subjects who are sedated with benzodiazepines. It assesses consciousness level in four areas: responsiveness, speech, facial expression, and eyes (Table 4.4). The OAA/S was validated in 18 healthy males 19–44 years of age, who received intravenous midazolam, initial dose 0.035 mg/kg, followed by additional doses of 0.015 mg/kg every 60–90 s until one of two levels of sedation was reached, light or heavy. A placebo group was also used, and two raters determined the depth

Table 4.3 Modified Ramsay Sedation Scale with American Academy of Pediatrics/Joint Commission/American Society of Anesthesiologists Designation

Score	Characteristics
1	Awake and alert, minimal or no cognitive impairment
2[a]	Awake but tranquil, purposeful responses to verbal commands at conversation level
3[a]	Appears asleep, purposeful responses to verbal commands at conversation level
4[b]	Appears asleep, purposeful responses to verbal commands but at louder than usual conversation level or requiring light glabellar tap
5[b]	Asleep, sluggish purposeful responses only to loud verbal commands or strong glabellar tap
6[c]	Asleep, sluggish purposeful responses only to painful stimuli
7[d]	Asleep, reflex withdrawal to painful stimuli only (no purposeful responses)
8[d]	Unresponsive to external stimuli, including pain

Source: Data from Ramsay et al. [9]
[a] Minimal
[b] Moderate
[c] Deep
[d] GA, general anesthesia

Table 4.4 The Observer's Assessment of Alertness/Sedation Scale

Assessment Categories				
Responsiveness	Speech	Facial expression	Eyes	Composite score level
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (Alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	–	–	2
Does not respond to mild prodding or shaking	–	–	–	1 (Deep sleep)

Source: Data from Chernik et al. [11]

of sedation using the OAA/S and 100 mm visual analog scale (VAS) rating patients from 0 (very sedated) to 100 (completely alert). Each subject was tested three separate times in a crossover design to assess the OAA/S reliability, criterion, and construct validity. The scale was found to be reliable with high correlations between raters, to have strong criterion and behavioral validity with consistently decreasing scores for placebo, light and heavy sedation. The construct validity among the four components was also strong, as was the validity for subsequent administration to the same subject in the crossover phase. Finally, the investigators also used two performance tests, the Digit Symbol Substitution Test, and the Serial Sevens Subtraction Test to compare to OAA/S scores and again found strong correlation.

Despite this thorough validation of the OAA/S in adult patients, and its use in several sedation research studies in children [12, 13], the OAA/S has not been separately validated in children. The OAA/S has been used in the validation of the University of Michigan Sedation scale [14], and in assessments of the reliability of the bispectral index monitor in children [15].

The Modified Observer Assessment Sedation Score (MOAA/S) uses only the responsiveness category of the OAA/S. This category was separately validated in the original study [11] but as with the OAA/S has not been separately validated in children.

The COMFORT Scale

The COMFORT Scale is a physiologically based scale that was originated and validated in children receiving intensive care, and as such is not completely applicable to the procedural sedation environment [16] (Table 4.5). It was tested and validated in 37 ventilated pediatric patients, and inter-rater agreement and internal consistency were very strong. Criterion validity, assessed by comparison with concurrent global ratings of PICU nurses, was also high. It is included here as an example of such a physiologically based scale. An added dimension is the assessment of pain or discomfort. Generally, a COMFORT score between 18 and 26, with each area scored as 2–3, is desirable to signify appropriate levels of sedation in the ICU setting. It is clear that this scale is complex and will require several minutes to assess, and as such is more applicable for ICU care where the scale is performed no more frequently than every hour. In the context of most procedural sedation this scale will be inappropriate.

The University of Michigan Sedation Scale

The University of Michigan Sedation Scale (UMSS) is an assessment tool that has been shown to be valid when compared to the OAA/S scale and other scales of sedation (Table 4.6) [14]. It is a level of consciousness tool that readily

Table 4.5 The COMFORT Score

Domain	Characteristics	Score
Alertness	Deeply asleep	1
	Lightly asleep	2
	Drowsy	3
	Fully awake and alert	4
	Hyper-alert	5
Calmness/agitation	Calm	1
	Slightly anxious	2
	Anxious	3
	Very anxious	4
	Panicky	5
Respiratory response	No coughing and no spontaneous respiration	1
	Spontaneous respiration with little or no response to ventilation	2
	Occasional cough or resistance to ventilator	3
	Actively breathes against ventilator or coughs regularly	4
	Fights ventilator; coughing or choking	5
Physical movement	No movement	1
	Occasional slight movement	2
	Frequent slight movement	3
	Vigorous movement limited to extremities	4
	Vigorous movement including torso and head	5
Blood pressure	Blood pressure below baseline	1
	Blood pressure consistently at baseline	2
	Infrequent elevations of 15% or more (1–3 observations)	3
	Frequent elevations of 15% or more (more than 3 episodes)	4
	Sustained elevation ≥15%	5
Heart rate	Heart rate below baseline	1
	Heart rate consistently at baseline	2
	Infrequent elevations of 15% or more (1–3 observations)	3
	Frequent elevations of 15% or more (more than 3 episodes)	4
	Sustained elevation ≥15%	5
Muscle tone	Muscle totally relaxed	1
	Reduced muscle tone	2
	Normal muscle tone	3
	Increased muscle tone and flexion of fingers and toes	4
	Extreme muscle rigidity and flexion of fingers and toes	5
Facial tension	Facial muscles totally relaxed	1
	Facial muscle tone normal; no facial muscle tension evident	2
	Tension evident in some facial muscles	3
	Tension evident throughout facial muscles	4
	Facial muscles contorted and grimacing	5

Source: Data from Ambuel et al. [16]

Table 4.6 University of Michigan Sedation Scale (UMSS)

Score	Characteristics
0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

separates patients into the sedation categories defined by the AAP, ASA, and Joint Commission. It does not explicitly rate pain, and does not include an assessment of vital signs. In a study of 32 children aged 4 months to 5 years undergoing CT scanning with oral chloral hydrate, 50–75 mg/kg, Malviya et al. [14] validated the UMSS by comparing the scores assessed every 10 min before, during, and after the procedure by the clinical sedation nurse, with assessments made

by trained, blinded observers of the videotaped assessments, which were edited and viewed in random order. UMSS was compared to a 10-point visual analog scale (VAS) and the OAA/S. One hundred and sixty-four observations were made, and the UMSS showed an excellent correlation with VAS ($r=0.955$) and OAA/S ($r=0.929$), $p<0.0001$ for both. There was excellent inter-rater agreement between sedation nurse and trained observers at UMSS 0 and 1, and good agreement at UMSS 3 and 4, as well as excellent agreement in a test–retest scenario where 75 videotaped observations were rescored at a later date. Thus it would appear that the UMSS meets several of the requirements for the ideal sedation scale, in that it is validated, rapid to administer, and allows repeated observations. A problem it shares with other scales is the need to arouse the patient to make an assessment; this is not possible during a procedure such as an MRI scanning sequence, and may be undesirable if the patient remains aroused after the assessment.

Dartmouth Operative Conditions Scale

The Dartmouth Operative Conditions Scale (DOCS) [1] was designed by three pediatrician/anesthesiologists, and then refined by videotaping 12 common procedures which included MRI, CT scan, voiding cystourethrogram, cardiac catheterization, fracture reduction, and bone marrow biopsy (Table 4.7). DOCS was created as a research tool to evaluate the conditions and responses to sedation [1]. The Dartmouth scale was validated by videotaping 95 procedures with sedation provided by a variety of providers including radiology nurses, pediatricians, pediatric residents, cardiologists, oncologists, and anesthesiologists. The scale allows quantification of children based on observable behavior. It rates level of sedation in four areas: pain or stress, movement, consciousness, and sedation side effects (Fig. 4.1). In this manner the completeness of the quality of sedation can be assessed comprehensively. Inter- and intra-rater reliability, construct validity, and criterion validity were all excellent. DOCS correlated well with the modified COMFORT score when video clips of procedural sedation were shown to 10 different healthcare providers.

The Dartmouth scale is a well-validated tool. It is best suited for research because of its comprehensive nature but nonetheless applicable to routine use for procedural sedation. Assessment of this scale at frequent intervals allows for careful tracking of state of sedation, effectiveness of sedation, uncontrolled side effects, and the timing of induction of sedation and recovery. This data can be helpful in quantifying the quality of sedation and best practices.

Modified Aldrete Score as a Sedation Scale

The Modified Aldrete Score has been in widespread use as a postanesthesia recovery score for many years and is detailed further in the latter part of this chapter (Table 4.8). Because of its

Table 4.7 The Dartmouth Operative Conditions Scale

Patient state	Observed behaviors/points			
Pain/stress	Eyes closed or calm expression: 0	Grimace or frown: 1	Crying, sobbing, or screaming: 2	–
Movement	Still: 0	Random little movement: 1	Major purposeful movement: 2	Thrashing, kicking, or biting: 3
Consciousness	Eyes open: 0	Ptosis, uncoordinated, or "drowsy": −1	Eyes closed: −2	–
Sedation side effects	SpO_2 <92%: −1	Noise with respiration: −1	Respiratory pauses >10 s: −1	BP decrease of >50% from baseline: −1

Source: Data from Cravero et al. [1]

near universal use for this purpose it is familiar to many sedation practitioners, and although not designed specifically for this purpose, it has been applied as a sedation scale during the procedure itself, as well as through recovery until discharge for procedural sedation in children. This score has not been independently validated neither in children nor for procedural sedation.

Processed EEG Monitors: The Bispectral Index

Several investigators have studied whether the Bispectral Index (BIS, Aspect Corporation, Newton, MA), a single-lead processed EEG that uses a proprietary algorithm to assign a number from 100 (completely awake) to 0 (isoelectric EEG), is meant to objectively assess the depth of sedation or anesthesia (Fig. 4.3). The appeal of processed EEG methods is that they are continuous, objective, and do not require awakening of the patient for assessment. Limitations of BIS include that the sensor, when applied to the forehead, must be secured with firm pressure to yield a valid signal, and this in itself may awaken the patient. Its ferromagnetic electrode array is not compatible with MRI magnetic fields. Malviya et al. [17] pooled data from four studies comparing UMSS to BIS values for 3,373 observations for 248 children aged 1 month to 18 years. The patients underwent a variety of diagnostic and therapeutic procedures, with a number of different agents including chloral hydrate, midazolam, pentobarbital, propofol, ketamine, and opioids. There was a moderate inverse correlation between BIS and UMSS in all age groups; however, there was not a difference between BIS values and UMSS 3 and 4 (moderate and deep sedation) in all age groups, and UMSS 0 and 1 (awake vs. light sedation) in infants. Furthermore, there was a poor correlation between BIS and UMSS with ketamine or opioid use. The authors concluded that BIS values must be interpreted with caution during procedural sedation in infants and children, with particular attention needed to the age of patient and agents used.

Mason et al. [18] compared BIS values immediately after an MRI or CT scan in 86 children greater than 1 year of age undergoing sedation with pentobarbital as a sole agent, who had achieved Ramsay scores of 4 or 5 (moderate or deep sedation). There was no significant difference between the sedation scores and BIS values (63 ± 12 and 64 ± 15 for RSS 4 and 5, respectively, $p = 0.64$). There was a wide variation in BIS values of 31–90. The authors concluded that the BIS had limited ability to distinguish moderate from deep sedation levels.

These studies and other data suggest that BIS has limited utility in assessing sedation level in children [19]. This is due to several factors, including the age-related developmental differences in the EEG between infants, children, and adults; and the different values achieved with similar levels of sedation with different agents [20].

Other Sedation Scales

There are a number of additional sedation scales, such as the Harris, modified Glasgow Coma Score, Cambridge, Bloomsbury, Neurobehavioral Assessment Scale, Sedation-Agitation Scale, PRST (pressure, rate, sweat, tearing), Vancouver Sedative Recovery Scale, Motor Activity Assessment Scale, and many others [10]. These scales are largely not applicable to pediatric procedural sedation because they were designed either for adult or for pediatric ICU care, and many have not been validated. None were designed primarily for procedural sedation. Most also measure physiologic variables as part of the assessment, and thus are long and cumbersome to apply for procedural sedation.

Objective, Physiologically Based Sedation Scales

As is evident from the discussion above, the ideal sedation scale for pediatric patients undergoing procedural sedation does not exist at this time. Limitations of all scales include the inherent subjectivity in assessing the patient's response to verbal or tactile stimulation, which is included in most of the scales. In addition, the arousal of the patient necessary for assessment can interfere with both

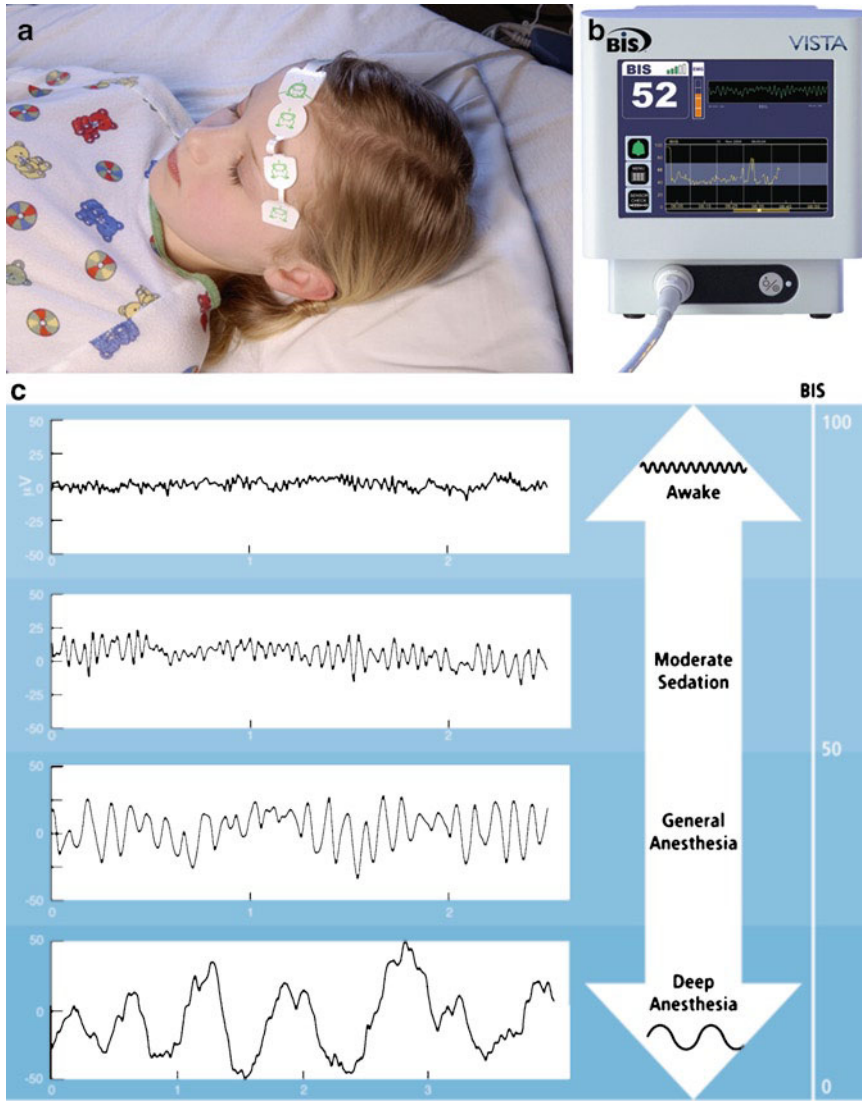

Fig. 4.3 (**a**) The Bispectral Index® (BIS) pediatric sensor. A one-channel EEG monitor with reference electrode applied to the forehead. (**b**) The BIS® monitor displays a single processed EEG number from 0 to 100, as well as the raw EEG waveform, and signal strength indicator. (**c**) The sedation continuum using the BIS algorithm. See text for details. (Images used by permission from Nellcore Puritan Bennett LLC, Boulder CO, doing business as Covidien)

the sedation level itself, and interrupt the procedure. Also, many scales have not been validated, and interobserver reliability is thus in question. Finally, the ability to discriminate safe from dangerous levels of sedation, i.e., deep sedation from general anesthesia, is limited and has not been demonstrated for most of the scales, or for processed EEG monitoring, and thus the goal of preventing airway and cardiovascular complications is also problematic using current schema.

Green and Mason [21] have advocated a reformulation of the sedation continuum. Instead of basing the scale on subjective or semiobjective criteria, scales based on objective physiologic monitoring would be devised. The reformulated sedation continuum would be based on an objective means of assessing and stratifying sedation risk. The tool would be identified as the Objective Risk Assessment Tool for Sedation (ORATS) and would guide training, credentialing and quality

New levels (as yet unnamed)	Escalating risk of serious adverse event	Physiological monitoring parameters (singular or combination)[a]	Recommended sedationist skill set	Recommended resources[b]
1	≤1:10,000	Consistent with normal awake pattern and frequency	Ability to observe and interpret the agreed-upon physiological monitoring parameters	Appropriate for risk level
2	1:1,000	← Objective monitoring predicts this level of risk	Skills appropriate for maintaining sedation at this risk level and for rescuing from the subsequent level	Appropriate for risk level
3	1:100	← Objective monitoring predicts this level of risk	Skills appropriate for maintaining sedation at this risk level and for rescuing from the subsequent level	Appropriate for risk level
4	≥1:10	← Objective monitoring predicts this level of risk	Skills appropriate for maintaining a patient at this risk level	Appropriate for risk level

Fig. 4.4 Objective Risk Assessment Tool for Sedation (ORATS). Preliminary sample schematic for an Objective Risk Assessment Tool for Sedation (ORATS). The choice of four levels here is arbitrary and for illustration purposes only; the final tool would contain the minimum number of discrete levels with independent predictive value.
[a]Focused research would be required to validate the specific variables, parameters, and thresholds that predict the progressive levels of serious adverse event risk. Evaluation of capnography, for example, could include but not be limited to evaluation of waveform, frequency, pattern and/or numerical value on inspiration or expiration.
[b]To be determined at each level by consensus panel and would include but not be limited to recommendations on adjuvant personnel, intravenous access, availability of rescue medications and airway equipment

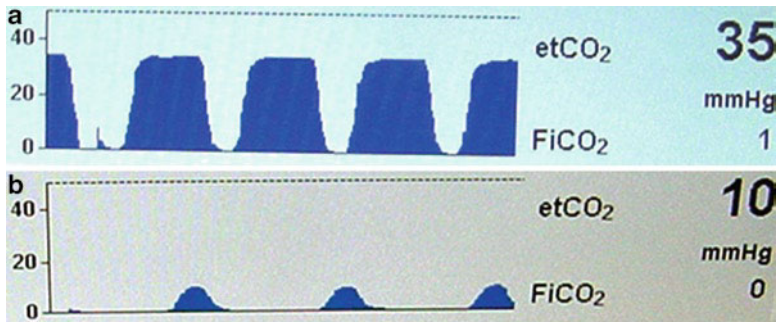

Fig. 4.5 (**a**) Normal capnograph in a sedated patient, obtained with divided nasal cannula. Respiratory rate of 16, and end-tidal CO_2 of 35 mmHg with full "area under the curve" waveform with long plateau signifies unobstructed airway and adequate tidal volumes in this patient. (**b**) Capnograph from a patient with significant respiratory depression. Respiratory rate is 10 per minute, and end-tidal CO_2 is only 10 mmHg, likely signifying small tidal volumes

indicators of sedation providers and sedation outcome respectively. This ORATS tool would be used in conjunction with a Comfort Assessment Tool for Sedation (CATS) which reconfigures the existing sedation continuum to reflect and follow the degree of comfort (Fig. 4.4) [22].

The scale includes capnography as one of the objective tools for assessment. Capnographic monitoring may provide an objective, valuable tool to follow sedation depth as well as warn of potential or existent compromise. Because most sedation-related adverse events begin with airway and ventilatory problems, capnography would be able to detect abnormalities, i.e., upper airway obstruction from lax pharyngeal muscle tone and tongue resulting in cessation of airflow, at its earliest occurrence (Fig. 4.5). This is substantially before arterial desaturation is detected by pulse oximetery, or bradycardia or hypotension from prolonged hypoxia. Portable capnographic monitoring is easily performed via widely available divided nasal cannulae made in infant, pediatric, and adult sizes, and can be used in all situations, including the MRI suite [23]. Indeed, capnography

monitoring for procedural sedation has been demonstrated to improve safety in children. Lightdale et al. [24] reported 174 moderate sedations in children for gastrointestinal endoscopy procedures, with half receiving capnographic monitoring and an intervention protocol and the other half blinded capnography with only rescue intervention, in a prospective randomized study design. Eleven percent of patients in the intervention arm had SpO_2 <95% for greater than 5 s, versus 24% in the control arm ($p<0.03$).

Potential capnographic criteria for increasing levels of sedation would include age-appropriate respiratory rate determined by the capnograph (slower means deeper sedation), significant decreases in end-tidal CO_2 values (signifying smaller tidal volumes or partial airway obstruction, or in worst case scenario low cardiac output), or complete absence of end-tidal CO_2, associated with complete airway obstruction. Specific, focused research would be required to stratify levels of risk based on capnographic and other parameters. A multidisciplinary effort would be required to develop updated guidelines.

Recovery and Discharge Scales

The concept of postanesthesia recovery after a surgical procedure has been expanded to procedural sedation, and scales originally designed to assess anesthesia recovery readiness for discharge to a hospital ward (Aldrete, Steward – see below) have also been expanded to include recovery from sedation, and readiness for discharge to home after procedural sedation without a painful operative procedure, e.g., an outpatient brain MRI for assessment of seizure disorder or developmental delay. Obviously the requirements for discharge can be very different in these two circumstances. The outpatient should be able to resume quiet "normal" activities before discharge from sedation, i.e., spontaneous wakefulness, eating, voiding, drinking, and ambulating with assistance. The inpatient may not need to meet all these requirements. This raises the question of whether these types of recovery scales have ever been validated for the purpose of discharge readiness, and in the case of the postanesthesia recovery scales, they have not. Besides assessing readiness to resume "normal" activities, the purpose of discharge and recovery scales is to prevent adverse events. Respiratory and cardiac events, including death, have occurred after premature discharge following procedural sedation [2]. These events have mostly occurred when a long lasting (long half-life) sedative such as chloral hydrate has been given. This can result in the child being unable to spontaneously unobstruct his or her airway.

Table 4.8 The modified Aldrete Scale

Domain	Response	Points
Activity	Able to move four extremities voluntarily or on command	2
	Able to move two extremities voluntarily or on command	1
	Unable to move extremities voluntarily or on command	0
Respiration	Able to breathe deeply and cough freely	2
	Dyspnea or limited breathing	1
	Apneic	0
Circulation	BP ± 20% of preanesthetic level	2
	BP ± 20–49% of preanesthetic level	1
	BP ± 50% of preanesthetic level	0
Consciousness	Fully awake	2
	Arousable on calling	1
	Not responding	0
O_2 saturation	Able to maintain SpO_2 >92% on room air	2
	Needs O_2 inhalation to maintain SpO_2 >90%	1
	SpO_2 <90% even with O_2 supplement	0

Source: Data from Aldrete [26]

The Aldrete score was introduced in 1970 [25], validated in adults, and quickly became the standard for PACU discharge from surgery for both adults and children. It rates five domains: activity, respiration, circulation, consciousness, and color. A point score of 0, 1, or 2 is given in each domain for a maximum score of 10 (Table 4.8). With the introduction of pulse oximetry, the score was modified to include SpO_2 instead of color [26]. Because of its familiarity, it has been used as a score for discharge from sedation as well. A score of 9 or 10 is standard to determine readiness for discharge.

The Maintenance of Wakefulness Test was devised to assess daytime somnolence in patients with sleep disorders [27, 28]. Polysomnography is used to measure the time taken for an adult patient to fall asleep in a dark, quiet room, after they have been instructed to stay awake. The Modified Maintenance of Wakefulness Test (MMWT) is a new modification of the original test, which was devised to help determine discharge readiness in children [29]. The MMWT requires visual observation to measure the duration of time from patient awakening to falling asleep. Malviya et al. studied 29 infants receiving either chloral hydrate or midazolam/diphenhydramine oral sedation for echocardiogram [29]. The modified wakefulness test was combined with the UMSS sedation scale (see above) to devise new, modified discharge criteria, which were compared with the standard hospital sedation discharge criteria. A UMSS of 0 or 1 (awake or minimally sedated), combined with a modified wakefulness test (MMWT) of 20 min, was required to meet these criteria. These data were compared with the Bispectral Index, with a value of 90 or higher signifying adequate wakefulness for discharge. Standard discharge criteria were stable vital signs, oxygen saturation, and level of consciousness compared to presedation baseline. The patient must be able to maintain a patent airway, manage oral secretions independently, or demonstrate the ability to swallow or demonstrate a gag reflex. In addition, the patient must be able to move or ambulate safely consistent with their presedation baseline. Combining the MMWT and UMSS criteria correctly identified 88% of infants with BIS >90, compared with only 55% of children assessed as "street ready" according to usual hospital discharge criteria [29]. In addition, time in recovery to discharge was only 16 ± 13 min using the standard discharge criteria versus 75 ± 76 min ($p \leq 0.007$) using the revised criteria. This study reveals that many children discharged using standard criteria may indeed not truly be back to their baseline status, and thus be potentially at risk for delayed complications. These more objective discharge criteria would need to be studied in a much larger group of patients to determine whether late complications were truly reduced.

Table 4.9 The Steward simplified postanesthetic recovery score

Domain	Level	Points
Consciousness	Awake	2
	Responding to stimuli	1
	Not responding	0
Airway	Coughing on command or crying	2
	Maintaining good airway	1
	Airway requires maintenance	0
Movement	Moving limbs purposefully	2
	Nonpurposeful movements	1
	Not moving	0

Source: Reprinted from Steward [30], with kind permission of Springer Science + Business Media

Steward [30], citing the difficulty of assessing patient color (pulse oximetry was not available at the time), and the sometimes inconsistent relationship of blood pressure to recovery from anesthesia, proposed a simplified score (Table 4.9). The original publication was a short description of the scale, and its rationale, but there was no actual patient data attempting to validate it as had been done in the original Aldrete Score paper. Despite its use in a number of pediatric studies [31, 32] it has not been independently validated.

Table 4.10 summarizes the sedation, recovery, and discharge scales which have been reviewed and include parameters assessed, utility in various phases of the sedation process, strengths and limitations.

A Practical Approach to Sedation Scales and Discharge Scores

Synthesizing the concepts presented in this chapter, and considering the demands of a busy sedation service that must be efficient as well as safe. I propose a practical approach to sedation scales, recovery and discharge scores. If moderate or deep sedation by a nonanesthesiologist is planned (the vast majority of pediatric sedations, as only older children undergoing nonpainful procedures, will undergo minimal sedation), one suggested approach is to use a validated simple level of consciousness scale (Ramsay, UMSS, or Aldrete).

Table 4.10 Characteristics of sedation and recovery/discharge scales

Scale	Parameters measured	Sedation, recovery, or discharge scale	Strengths	Limitations	Validated?	References
Ramsay Sedation Scale	Level of consciousness	S, R, D	Simple	No physiologic parameters, must awaken patient	Adults	[6, 9, 10]
OAA/S	Responsiveness, speech, facial expression, eyes	S, R, D	Well validated, relatively simple	No physiologic parameters, must awaken patient	Adults	[11–13]
Modified OAA/S	Responsiveness only	S, R, D	Simple	No physiologic parameters, must awaken patient	Adults	[11]
COMFORT	Alertness, agitation, and multiple physiologic parameters	S	Comprehensive, well validated	Very complex, time consuming, not appropriate for routine procedural sedation	Children	[16]
UMSS	Level of consciousness	S, R, D	Relatively simple	Does not rate pain or physiologic parameters, must arouse patient	Children	[14]
Dartmouth	Pain, movement, consciousness, physiologic parameters	S	Comprehensive, rates pain and movement	Relatively complex	Children	[1]
Modified Aldrete	Activity, respiration, circulation, consciousness, oxygen saturation	S, R, D	Widespread use and familiarity	Not designed as a sedation scale	Adults	[25, 26]
Modified Maintenance of Wakefulness	Maintenance of alertness	R, D	Simple	Requires at least 20 min to administer	Children	[29]
Steward	Consciousness, airway, movement	S, R, D	Simple	No assessment of oxygen saturation	No	[30]
Bispectral Index®	Processed electroencephalogram	S, R, D	Semiobjective; one simple number reported	Continuous, no need to awaken patient	Adults, incomplete validation in young children; not compatible with MRI	[17–19]
Capnography-based	End-tidal CO_2	S, R	Objective; sensitive indicator of respiratory depression/obstruction	Many artifacts; equipment not always available	Adults and children, as monitor	[21–24]

S sedation phase; *R* recovery phase; *D* discharge phase; *OAA/S* Observer's Assessment of Alertness/Sedation Scale; *UMSS* University of Michigan Sedation Scale

Assess every 15 min at a minimum, or when a change in level of sedation occurs, i.e., after an additional dose of sedative. In addition to standard monitoring with continuous ECG and SpO_2, document automated oscillometric blood pressure measurement at least every 5 min. The sedation and recovery personnel must be familiar with the patient's baseline heart rate, blood pressure, respiratory rate and oxygen saturation, as well as the age-related normal ranges. Follow end-tidal CO_2 monitoring via a divided nasal cannula for moderate sedation and beyond, if logistically and practically feasible. The sedation scale need not be assessed if it would arouse the patient and interrupt the procedure, on a patient who has not exhibited any signs of oversedation, i.e., hypotension or respiratory depression. In this way, the frequent physiologic monitoring is used instead of a more extensive and difficult to administer scale that scores the vital signs, i.e., COMFORT scale. The recovery and discharge score could be a modified Aldrete score of 9 or 10, a UMSS of 0 or 1, or a modified wakefulness test of 20 min. It may be simplest to use the same scale for both the sedation and the recovery phases, i.e., the Ramsey, UMSS, or modified Aldrete could be used throughout. The exact tests and scales are determined by institutional preferences.

Whatever scales are decided upon, they are not a substitute for well-trained sedation practitioners exercising skill and vigilance, combined with continuous physiological monitoring to ensure the best outcomes.

Conclusions

Regular use of sedation, recovery, and discharge scales for pediatric procedural sedation is essential, given the wide variety of practitioners involved, as well as the variety of procedures and agents. Uniform assessment will minimize oversedation and complications, but also ensure that adequate levels of sedation and analgesia are achieved. In addition, only by more objective measurement of sedation will hospitals and departments have accurate data to improve the quality and outcomes of their programs. In the future, more objective physiologically based scales, utilizing capnography, should be devised. Any research on new agents or approaches must be validated using sedation scores that are objective and allow scientific comparison of different methods.

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Physiological Monitoring for Procedural Sedation: The Routine and Beyond

5

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Introduction

Physiological monitoring of vital signs is essential for the safe practice of procedural sedation and analgesia. Oxygenation, ventilation, cortical activity, and hemodynamics can all be monitored noninvasively in spontaneously breathing patients. This chapter discusses the current guidelines and standards for patient monitoring and the essential monitoring modalities for procedural sedation and analgesia in children.

Current Guidelines and Standards

There are numerous procedural sedation and analgesia guidelines that have been created by specialty societies to standardize procedural sedation and analgesia practice in order to optimize patient safety (Table 5.1) [1]. The most widely disseminated guidelines are from the American Academy of Pediatrics [2], the American Society of Anesthesiologists [3], and the American College of Emergency Physicians [4]. In the early 1990, the Joint Commission took a special interest in procedural sedation and analgesia, and in 2001 released standards for pain management, sedation, and anesthesia care, with the central theme that sedation care should be comparable throughout a given hospital [5]. Patients sedated in settings outside the operating room should not receive a significantly different level of attention or monitoring than those sedated for a similar procedure in the operating room. To ensure this, the Joint Commission requires specific procedural sedation and analgesia protocols that apply consistently throughout each institution. These hospital-wide sedation policies vary from site to site based upon the specific needs and resources available within each institution.

At each hospital accreditation survey, the Joint Commission will evaluate whether clinicians practice procedural sedation and analgesia consistent with their hospital-wide sedation policy, and whether they provide sufficient documentation for such compliance. Physicians must be familiar with their hospital's sedation policies, and should work with their medical staff to ensure that such policies are suitably detailed. Most hospitals pattern their sedation policies after the Joint Commission standards and definitions.

The Joint Commission requires that practitioners who are permitted to administer deep sedation must be qualified to rescue patients from general anesthesia. Moderate sedation suffices for the majority of procedures in cooperative children, although it will not be adequate for extremely painful procedures, or in uncooperative patients. Deep sedation can facilitate these, but at greater risk of cardiorespiratory depression than moderate sedation [3, 5] (Table 5.2).

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Table 5.1 Specialty societies with published sedation guidelines

American Academy of Pediatrics
American Academy of Pediatric Dentistry
American Academy of Periodontology
American Association of Critical-Care Nurses
American College of Critical Care Medicine
American College of Emergency Physicians
American Nurses Association
American Society for Gastrointestinal Endoscopy
American Society of Anesthesiologists
American Society of Plastic and Reconstructive Surgeons
Association of Operating Room Nurses
Emergency Nurses Association
Joint Commission on Accreditation of Healthcare Organizations
National Institutes of Health
Society of Gastroenterology Nurses and Associates
Society of Nuclear Medicine

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Table 5.2 Levels of sedation

Minimal sedation (anxiolysis) [7]: A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
Moderate sedation (formerly "conscious sedation") [7]: A drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. Reflex withdrawal from a painful stimulus is not considered a purposeful response. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
Dissociative sedation [50, 51]: A trance-like cataleptic state induced by the dissociative agent ketamine characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.
Deep sedation [7]: A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
General anesthesia [7]: A drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

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Observational Monitoring

Physiological monitoring has two components: observational monitoring by a designated clinician and electronic monitoring with mechanical monitoring devices. The most important element of procedural sedation and analgesia monitoring is close and continuous patient observation by an individual capable of recognizing adverse events. This person must be able to continuously observe the patient's face, mouth, and chest wall motion, and equipment or sterile drapes must not interfere with such visualization. This careful observation will allow prompt detection of adverse events such as respiratory depression, apnea, airway obstruction, emesis, and hypersalivation [6]. An individual with advanced life-support skills should be immediately available in all settings where deep sedation is performed.

During deep sedation, the individual dedicated to patient monitoring should be experienced with this depth of sedation and have no other responsibilities that would interfere with the required advanced level of monitoring and documentation. Individual hospital-wide sedation policies may have additional requirements for how and when deep sedation is administered based on their specific needs and available resources.

Vital signs should be measured at individualized intervals including at baseline, after drug administration, on completion of the procedure, during early recovery, and at completion of recovery. During deep sedation, vitals signs should be assessed every 5 min. In addition to recording vital signs at set intervals, clinicians must be especially vigilant during key phases of the sedation. Patients are usually at highest risk of complications 5–10 min following administration of IV medications and during the immediate post-procedure period when external stimuli are discontinued.

Electronic Monitoring

The use of electronic monitoring has greatly enhanced the safety of procedural sedation and analgesia. Continuous oxygenation (pulse oximetry with an audible signal), ventilation (capnography), and hemodynamics (blood pressure and electrocardiogram (ECG)) can all be monitored noninvasively in spontaneously breathing patients.

Oxygenation Monitoring

Pulse oximetry is the noninvasive measurement of the percent of hemoglobin bound to oxygen providing a continuous means of estimating in real-time the arterial oxygen saturation. The underlying principles of oximetry were developed in 1932 based on the Beer–Lambert law (the concentration of an unknown solute dissolved in a solvent can be determined by light absorption). Modern pulse oximetry technology, using optical plethysmography and spectrophotometry, was invented in 1974 and completed in 1980 with the addition of a probe and a miniaturized computer in the monitor [7]. The probe, consisting of red and infrared (IR) light sources and a photoelectric detector, is positioned across a pulsatile vascular bed such as the finger, the foot, or ear lobe [7, 8].

The most common type of oximetry (i.e., transmission oximetry) places the light sources on one side of the tissue bed and the photodetector on the opposite side. The pulsatile variation of the emitted red and IR light transmitted through the tissue bed is accessed by the oximeter which divides the signal into an arterial blood pulsatile component and a nonpulsatile component (venous and capillary blood). Data averaged over several arterial pulse cycles are represented as the oxygen saturation (SpO_2) [7–9]. There is a tight correlation between the arterial hemoglobin oxygen saturation (PaO_2) and the SpO_2 in a nonlinear fashion as described by the oxyhemoglobin dissociation curve (Fig. 5.1) [8–10]. The shape of the curve has important clinical implications. In the hypoxic patient, small changes in SpO_2 on the steep part of the curve result in large changes in the PaO_2, while SpO_2 values at high levels of

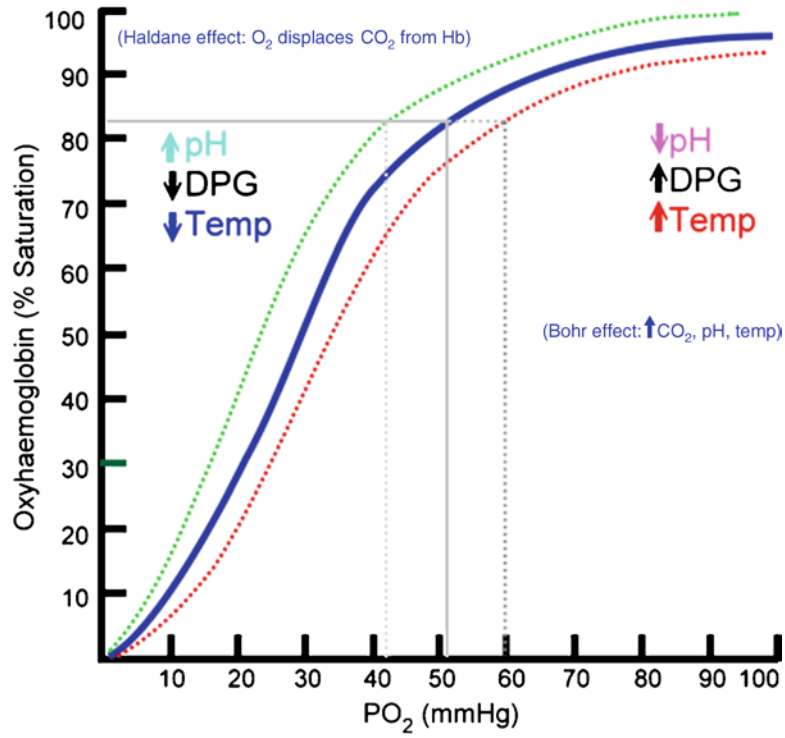


Fig. 5.1 Oxyhemoglobin dissociation curve

oxygenation (on the plateau of the curve) are relatively insensitive at detecting significant changes in PaO_2.

Patients with normal lung function and adequate gas exchange have an SpO_2 between 97 and 100%. Pulse oximeters are accurate for saturations >70% [10]. When SaO_2 falls below 95%, hypoxia may be present, although patients with obstructive lung disease may live in this range [8, 9]. Oxygen saturations below 90% represent significant hypoxia. At 75% saturation, oximetry bias is uniformly scattered (7% underestimation and 7% overestimation).

The finger is the most common probe site used for pulse oximetry. If the finger is inaccessible or unsuitable, other probe sites, such as the ear lobe or the bridge of the nose, may be used. In neonates and infants, probes sites include the great toe, the heel, the sole, and the lateral aspect of the foot.

There are a number of important limitations to the accuracy of pulse oximetry: poor perfusion secondary to severe vasoconstriction (e.g., low perfusion states, shock, hypothermia), artifact from excessive patient motion, severe anemia, high-intensity ambient light, abnormal hemoglobins, venous pulsations, synthetic fingernails and nail polish, or intravenous dyes [8, 10]. Recent advances in motion control technology have made pulse oximetry more reliable during patient motion. Carboxyhemoglobin (COHb) and methemoglobin (MetHb) contribute to light absorption and cause errors in saturation readings. The oximeter sees COHb as though it were mostly OxyHb and gives a false high reading. In the presence of high levels of MetHb, the SpO_2 is erroneously low when the arterial saturation is above 85% and erroneously high when the arterial saturation is below 85%. MetHb produces a large pulsatile absorbance signal at both the red and IR wavelengths. This forces the absorbance ratio toward unity, which corresponds to a SpO_2 of 85%. Further, in dark-skinned patients, false high readings and a higher incidence of failure of signal detection have been reported [8–10].

Pulse oximetry is not a substitute for ventilation monitoring, as there is a lag time, the extent of the lag depending on the age and physical status of the patient, between the onset of hypoventilation or apnea and a change in oxygen saturation. Therefore, during procedural sedation, ventilation monitoring should always accompany oxygenation monitoring. Hypoventilation and resultant hypercapnia may precede a decrease in hemoglobin O_2 saturation by minutes [11]. Further, supplemental O_2 may mask hypoventilation by delaying the eventual O_2 desaturation for which pulse oximetry monitoring is designed to recognize [12].

Ventilation Monitoring

Capnography is the noninvasive measurement of the partial pressure of carbon dioxide in exhaled breath represented as a numerical value (end-tidal CO_2) and a waveform. The CO_2 waveform or capnogram represents changes in the CO_2 concentration over the time of one respiratory cycle (Fig 5.2) [13]. Changes in the shape of the waveform are diagnostic of disease conditions, while changes in end-tidal CO_2 ($EtCO_2$ – the maximum CO_2 concentration at the end of each tidal breath) can be used to assess disease severity and response to treatment [14].

Modern capnography was developed in the 1940s and commercialized in the 1960s and 1970s with the development of mass spectroscopy. Capnography became a routine part of anesthesia practice in Europe in the 1970s and in the United States in the 1980s [13]. Most capnography technology is built on infrared (IR) radiation techniques and based on the fact that CO_2 molecules absorb IR radiation at a specific wavelength, with the amount of radiation absorbed having a close to exponential relation to the CO_2 concentration

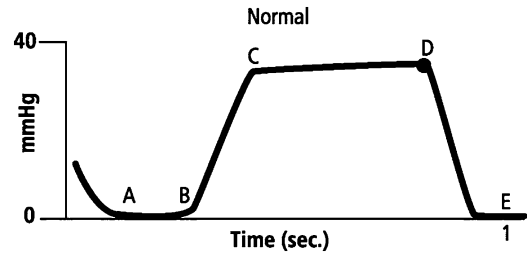


Fig. 5.2 Normal CO_2 waveform

present in the breath sample. Detecting changes in IR radiation levels with photodetectors allows for the calculation of the CO_2 concentration in the gas sample.

Carbon dioxide monitors measure gas concentration or partial pressure using one of two configurations: mainstream or sidestream. Mainstream devices measure CO_2 directly from the airway, with the sensor located on the endotracheal tube. Sidestream devices measure CO_2 by aspirating a small sample from the exhaled breath through tubing to a sensor located inside the monitor. Mainstream systems, as the sensor is located on the endotracheal tube, are configured for intubated patients. Sidestream systems, as the sensor is located inside the monitor, are configured for both intubated and non-intubated patients. The airway interface for intubated patients is an airway adapter placed on the hub of the endotracheal tube; and for spontaneously breathing patients, an nasal-oral cannula which allows concomitant CO_2 sampling and low-flow oxygen delivery.

Sidestream systems can be either high flow (with 150 cc/min as the amount of CO_2 in the breath sample required to obtain an accurate reading) or low flow (50 cc/min). Low-flow sidestream systems have a lower occlusion rate (from moisture or patient secretions) and are more accurate in patients with low tidal volumes (neonates, infants, and patients with hypoventilation and low tidal volume breathing) [15]. In high-flow systems, when the tidal volume of the patient drops below 150 cc (i.e., the flow rate of the system), the monitor will entrain room air to compensate, falsely diluting the $EtCO_2$ [16–18].

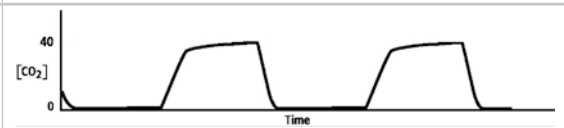
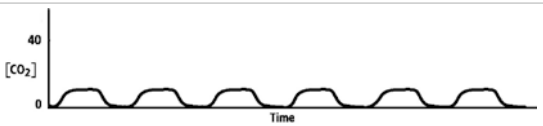
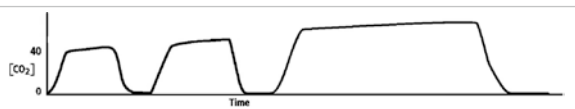
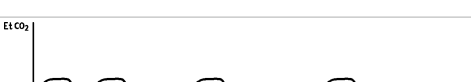
The CO_2 waveform, corresponding to a single breath, consists of four phases [2, 15]. Phase 1 (dead space ventilation, A–B) represents the beginning of exhalation where the dead space is cleared from the upper airway. Phase 2 (ascending phase, B–C) represents the rapid rise in CO_2 concentration in the breath stream as the CO_2 from the alveoli reaches the upper airway. Phase 3 (alveolar plateau, C–D) represents the CO_2 concentration reaching a uniform level in the entire breath stream and concludes with a point of maximum CO_2 concentration ($EtCO_2$). Phase 4 (D–E) represents the inspiratory cycle where the CO_2 concentration drops to zero as atmospheric air enters the airway (Fig. 5.2). A normal waveform is characterized by four distinct phases, a CO_2 concentration that starts at zero and returns to zero (i.e., there is no rebreathing of CO_2), and a maximum CO_2 concentration reached with each breath (i.e., $EtCO_2$).

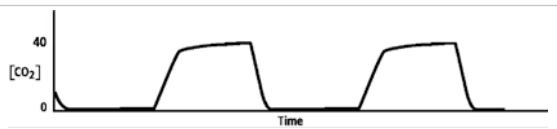
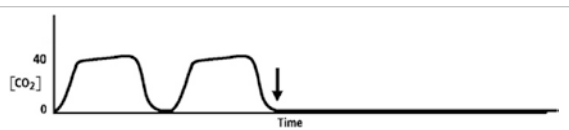
Patients with normal lung function have a characteristic rectangular shaped waveform and a narrow $EtCO_2$–pCO_2 gradient (0–5 mmHg), with the $EtCO_2$ accurately reflecting the $PaCO_2$ [14, 19]. Patients with obstructive lung disease will have a more rounded ascending phase and an upward slope in the alveolar plateau (Table 5.3) [20]. In patients with abnormal lung function secondary to ventilation–perfusion (V–Q) mismatch, the gradient will widen, depending on the severity of the lung disease [21–23].

The shape of the waveform is affected by the $EtCO_2$ and the expiratory time. The amplitude of the waveform is determined by the $EtCO_2$ value and the width is determined by the expiratory time. Hyperventilation (increased respiratory rate, decreased $EtCO_2$) results in a low amplitude and narrow waveform, while classical hypoventilation (decreased respiratory rate, increased $EtCO_2$) results in a high amplitude and wide waveform (Table 5.3). Acute bronchospasm results in a waveform with a curved ascending phase and upsloping alveolar plateau (Table 5.3). An $EtCO_2$ >70 mm Hg, in patients without chronic hypoventilation, indicates respiratory failure.

Capnography provides a continuous, breath-by-breath measure of respiratory rate and CO_2 exchange and can detect the common adverse airway and respiratory events associated with procedural sedation and analgesia [24]. Capnography is the earliest indicator of airway or respiratory compromise and will manifest an abnormally high or low $EtCO_2$ well before pulse oximetry detects a falling oxyhemoglobin saturation, especially in patients receiving supplemental oxygen. Early detection of respiratory compromise is especially important in infants and toddlers who have smaller functional residual capacity and greater oxygen consumption relative to older children and adults. Capnography provides a non-impedance respiratory rate directly

Table 5.3 Capnographic airway assessment for procedural sedation and analgesia

Diagnosis	Waveform	Features		Intervention
Normal		SpO_2 $EtCO_2$ Waveform RR	Normal Normal Normal Normal	No intervention required Continue sedation
Hyperventilation		SpO_2 $EtCO_2$ Waveform RR	Normal ↓ Decreased amplitude and width ↑	
Bradypneic hypoventilation (Type 1)		SpO_2 $EtCO_2$ Waveform RR	Normal ↑ Increased amplitude and width ↓↓↓	Reassess patient Continue sedation
		SpO_2 $EtCO_2$ Waveform RR	↓ ↑ Increased amplitude and width ↓↓↓	Reassess patient Assess for airway obstruction Supplemental oxygen Cease drug administration or reduce dosing
Hypopneic hypoventilation (Type 2)		SpO_2 $EtCO_2$ Waveform RR	Normal ↓ Decreased amplitude ↓	Reassess patient Continue sedation
		SpO_2 $EtCO_2$ Waveform RR	↓ ↓ Decreased amplitude ↓	Reassess patient Assess for airway obstruction Supplemental oxygen Cease drug administration or reduce dosing
Hypopneic hypoventilation with periodic breathing		SpO_2 $EtCO_2$ Waveform RR Other	Normal or ↓ ↓ Decreased Amplitude ↓ Apneic pauses	

Physiological variability		SpO_2 $EtCO_2$ Waveform RR	Normal Normal Varying[a] Normal	No intervention required Continue sedation	
Bronchospasm		SpO_2 $EtCO_2$ Waveform RR Other	Normal or ↓ Normal, ↑, or ↓[b] Curved Normal, ↑ or ↓[b] Wheezing	Reassess patient Bronchodilator therapy Cease drug administration	
Partial airway obstruction Partial laryngospasm		SpO_2 $EtCO_2$ Waveform RR Other	Normal or ↓ Normal Normal Variable Noisy breathing and/or inspiratory stridor	Full airway patency restored with airway alignment Noisy breathing and stridor resolve	Reassess patient Establish IV access Supplemental O_2 (as needed) Cease drug administration
				Airway not fully patent with airway alignment Noisy breathing and stridor persist	
Apnea		SpO_2 $EtCO_2$ Waveform RR Other	Normal or ↓[c] Zero Absent Zero No chest wall movement or breath sounds	Reassess patient Stimulation Bag mask ventilation Reversal agents (where appropriate) Cease drug administration	
Complete airway obstruction Complete laryngospasm		SpO_2 $EtCO_2$ Waveform RR Other	Normal or ↓[c] Zero Absent Zero Chest wall movement and breath sounds present	Airway patency restored with airway alignment Waveform present	
				Airway not patent with airway alignment No waveform	Positive pressure ventilation

Source: From Krauss and Hess [24]
[a]Varying waveform amplitude and width
[b]Depending on duration and severity of bronchospasm
[c]Depending on duration of episode

from the airway (via oral-nasal cannula) that is more accurate than impedance-based respiratory monitoring. In patients with obstructive apnea, impedance-based monitoring will interpret chest wall movement without ventilation as a valid breath.

Both central and obstructive apnea can be rapidly detected by capnography (Table 5.3). Loss of the waveform, in conjunction with no chest wall movement and no breath sounds confirms the diagnosis of central apnea. Obstructive apnea is characterized by loss of the waveform, chest wall movement, and absent breath sounds. The absence of the waveform in association with the presence or absence of chest wall movement distinguishes apnea from upper airway obstruction and laryngospasm. Response to airway alignment maneuvers can further distinguish upper airway obstruction from laryngospasm.

There are two types of drug-induced hypoventilation that occur during procedural sedation and analgesia (Table 5.3) [24]. Bradypneic hypoventilation, commonly seen with opioids, is characterized by an increased $EtCO_2$ and an increased $PaCO_2$. Respiratory rate is depressed proportionally greater than tidal volume resulting in bradypnea, an increase in expiratory time, and a rise in $EtCO_2$, graphically represented by a high amplitude and wide waveform (Table 5.3). Bradypneic hypoventilation follows a predictable course with $EtCO_2$ increasing progressively until respiratory failure and apnea occur. Although there is no absolute threshold at which apnea occurs, patients without chronic hypoventilation with $EtCO_2$ >70 mmHg are at significant risk.

Hypopneic hypoventilation, commonly seen with sedative-hypnotic drugs, is characterized by a normal or decreased $EtCO_2$ and an increased $PaCO_2$ as airway dead space remains constant and tidal volume is decreasing (Table 5.3). Tidal volume is depressed proportionally greater than respiratory rate, resulting in low tidal volume breathing that leads to an increase in airway dead space fraction (dead space volume/tidal volume). As tidal volume decreases, airway dead space fraction increases which in turn results in an increase in the $PaCO_2$–$EtCO_2$ gradient. Even though $PaCO_2$ is increasing, $EtCO_2$ may remain normal or be decreasing, graphically represented by a low amplitude waveform (Table 5.3). Hypopneic hypoventilation follows a variable course and may remain stable with low tidal volume breathing resolving over time as CNS drug levels decrease and redistribution to the periphery occurs, progress to periodic breathing with intermittent apneic pauses (which may resolve spontaneously or progress to central apnea), or progresses directly to central apnea.

The low tidal volume breathing that characterizes hypopneic hypoventilation increases dead space ventilation when normal compensatory mechanisms are inhibited by drug effects. Minute ventilation, which normally increases to compensate for an increase in dead space, does not change or may decrease [25]. As minute ventilation decreases, PaO_2 decreases. If minute ventilation decreases further, oxygenation is further impaired [26, 27]. However, $EtCO_2$ may initially be high (bradypneic hypoventilation) or low (hypopneic hypoventilation) without significant changes in oxygenation, particularly if supplemental oxygen is given. Therefore, a drug-induced increase or decrease in $EtCO_2$ does not necessarily lead to oxygen desaturation and may not require intervention.

Technical problems with capnography have limited its effectiveness and restricted its clinical applications. These problems include: interference with the sensor by condensed water and patient secretions, cross sensitivity with anesthetic gases in conventional CO_2 sensors, lack of ruggedness for intra- and interhospital transport, and power consumption issues related to portable battery operation time. These issues have been resolved in the newer generation capnography monitors. Early capnography airway interfaces (i.e., nasal cannula) had difficulty providing consistent measurements in mouth breathing patients and patients who alternated between mouth and nose breathing. The newer oral-nasal interfaces do not have these problems.

Hemodynamic Monitoring

Noninvasive blood pressure (NIBP) measurement is an automated method of repetitively determining blood pressure that is accurate in

both adults and children. Blood pressure can be obtained manually (only when the operator pushes a button) or automatically cycled at preset intervals with the cuff inflated to specific levels. NIBP provides a display of the heart rate, systolic, diastolic, and mean blood pressures by electronically determining the pulse amplitude. During deflation, the cuff determines the amplitude of the pulsations transmitted by movement of arterial wall under the cuff. A sudden rise in the magnitude of the pulsations accompanies the artery opening and represents the systolic pressure. The magnitude of the pulsations increases to a peak and then falls rapidly. The diastolic pressure is determined at the point where there are no further alterations in the magnitude of the pulsations. The accuracy of NIBP depends on utilizing the correct cuff size (especially important in children and obese patients) and on minimizing patient motion during measurement.

Continuous ECG monitoring is useful for the rapid detection of rhythm disturbances or ischemia. Continuous ECG monitoring for procedural sedation and analgesia is neither mandatory nor standard of care in patients without a cardiovascular disease. However, such monitoring is simple, inexpensive, and readily available and is frequently used during procedural sedation and analgesia in children.

Depth of Sedation Monitoring

Monitoring modalities that measure the brain's response to anesthetic agents have recently been studied for use in procedural sedation and analgesia [28–30]. Although these technologies have been used to monitor depth of sedation/anesthesia in the operating room, in 2006 the American Society of Anesthesiologists concluded that the clinical applicability in the operating room "has not been established" [31]. Further, the predictive value of this type of monitoring for the moderate and deep sedation outside the operating room remains unclear.

The most studied of these technologies is the bispectral index (BIS), that uses a processed electroencephalogram (EEG) signal to quantify sedation depth. A BIS value of 100 is considered complete alertness, a range of 40–60 consistent with general anesthesia and zero is no cortical activity [32].

Several studies have shown a reasonable correlation between BIS and standard observational sedation score in children older than 6 months (i.e., University of Michigan Sedation Scale (UMSS), Observer's Assessment of Alertness/Sedation (OAA/S), Ramsey Score) for commonly used sedatives such as midazolam, pentobarbital, chloral hydrate, and propofol. However, other studies have failed to consistently validate a tight correlation between BIS values and specific levels of sedation as measured by standard observational sedation scores.

A 2007 study of 248 children (1 month to 18 years), using pooled raw data from four independently conducted studies, found a moderate correlation between BIS and UMSS with the use of chloral hydrate, pentobarbital, propofol, and midazolam, but poor correlation with ketamine and with opioids. Bispectral index values were significantly lower for a same observed level of sedation with propofol and pentobarbital when compared to midazolam and chloral hydrate, making BIS an unreliable method of reaching a desired level of sedation [33]. The poor correlation observed with opioids is thought to be secondary to opioids providing sedation without hypnosis [33, 34]. Hence, it has been argued that BIS reflects cortical activity rather than level of consciousness [35].

Overly et al, in a study of 47 patients treated either with ketamine/midazolam, methohexital, propofol, or midazolam and a narcotic found a good correlation between BIS and OAA/S scale for non-dissociative agents, but not with ketamine [36]. Ketamine sedation, in multiple studies, has shown an unreliable correlation between BIS and standard sedation scoring, with persistence of high BIS or even an increase in BIS despite achieving deeper levels of sedation [33, 34, 36].

Dexmedetomidine, a selective alpha-2 adrenergic agonist that provides sedation without respiratory depression, has shown to correlate well with standard observational sedation scores. In a study of 11 mechanically ventilated children in an intensive care unit setting sedated with dexmedetomidine, significant correlations between

Richmond agitation sedation scale and BIS values were found [37].

A 2009 crossover study of nine adult volunteers receiving propofol or dexmedetomidine followed by the alternate drug 7 days later also showed good correlation between BIS and OAA/S. However, for a same OAA/S score, BIS values were significantly lower in patients sedated with dexmedetomidine suggesting that the BIS score is drug-specific with different scores signifying different levels of sedation for different sedation agents [38].

Bispectral index scores in infants less than 6 months of age have been noted to be unreliable during general anesthesia and procedural sedation, likely secondary to the fact that the BIS algorithm was developed using adult EEG data [34, 39].

In summary, procedural sedation studies using BIS monitoring have found unacceptably wide ranges of BIS values at various depths of sedation that did not correlate with standard sedation scores (e.g., Ramsey Score) [28–30]. As BIS does not reliably gauge depth in individual patients, it cannot currently be recommended for use in procedural sedation and analgesia.

Cerebral Oximetry

Another new technology with potential application to procedural sedation is cerebral oximetry. Through near-infrared spectroscopy, cerebral tissue oxygenation (i.e., regional oxygen saturation, rSO_2) is measured by monitoring the nonpulsatile signal component reflecting tissue circulation of arterioles, capillaries, and venules. Unlike conventional pulse oximetry, which monitors the pulsatile signal component reflecting arterial circulation, cerebral oximetry is reliable in low perfusion states, shock, and cardiac arrest. Cerebral oximetry represents a "weighted average" of the tissue circulation and reflects a potentially more accurate measurement of oxygen consumption, similar to and correlating with mixed venous saturations [40, 41].

Cerebral oximetry has been primarily studied in the operating room, except for a recent ED procedural sedation study, which demonstrated poor correlation between cerebral oximetry, pulse oximetry, and capnography [42]. In this study, 100 children of ages 9 months to 18 years were sedated with various agents (ketamine, fentanyl, pentobarbital, dexmedetomidine, or propofol). Changes in rSO_2 occurred in 2.1% of patients and were associated with changes in SpO_2 23% of the time and changes in end-tidal CO_2 29% of the time. Only a minority of hypoxic episodes resulted in a decrease in rSO_2, while the majority of changes in rSO_2 occurred in the absence of changes in cardiorespiratory parameters.

Although rSO_2 appears to be a more sensitive measure of cerebral oxygenation than pulse oximetry, isolated decreases in rSO_2 do not appear to correlate well with short or long-term neurological outcome, as illustrated in a small study of adult patients undergoing carotid endarterectomy. Importantly, there is no clear rSO_2 threshold under which clinically significant brain hypoxia occurs [43].

Noninvasive Cardiovascular Monitoring

Methods for advanced noninvasive cardiovascular monitoring continue to be refined. Through thoracic electrical bioimpedance, and similar to impedance cardiography, electrical cardiometry (or electrical velocimetry) enables the measurement of various cardiac parameters including cardiac output, cardiac index, stroke volume, systemic vascular resistance, and index of contractility. Such methods rely on the interpretation of a signal from sensors placed on the neck and chest, which quantify changes in conductivity of the blood in the aorta during the cardiac cycle [44–46].

Electrical velocimetry measurements have been shown to correlate with measurements derived from the Fick principle applied to blood sampled invasively in pediatric patients with congenital heart disease undergoing left heart catheterization [47], and to transesophageal echocardiography in ventilated children following cardiac surgery – although electrical velocimetry appeared to underestimate cardiac output

in terms of absolute values [48]. Impedance cardiography has shown good correlation with standard pulmonary artery thermodilution methods during cardiac surgery [49]. At present, the applicability and clinical relevance of advanced noninvasive cardiovascular monitoring to pediatric procedural sedation remains unclear.

Summary

There have been significant advances in noninvasive physiological monitoring of ventilation, oxygenation, and hemodynamics for procedural sedation in children with the advent of improved motion control for pulse oximetry, low-flow capnography systems, the potential of regional cerebral oximetry, and entropy depth of sedation monitoring. These systems bring enhanced safety and efficiency to pediatric procedural sedation.

Future directions in pediatric procedural sedation will include easier methods to integrate the expanding physiological monitoring data now available to the clinician (sophisticated methods for data display, interpretive algorithms, composite indices based on integration of physiological parameters), and new noninvasive technology to monitor blood pressure, vascular tone, cardiac output, cerebral activity, and oxygenation.

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The Pediatric Airway: Anatomy, Challenges, and Solutions

6

Lynne R. Ferrari

One of the most important aspects of planning sedation is consideration of the airway of each individual patient. Sedation may alter laryngeal anatomy, function, and respiratory mechanics therefore, it is essential that the practitioner have a thorough understanding of the pediatric airway.

Anatomy of the Pediatric Airway

Airway compromise in the infant or child may result from abnormalities in nasal cavities, nasopharynx, oral cavity, pharynx, and neck. The airway is comprised of the larynx, trachea, bronchi, and alveoli. The trachea in the infant is smaller than that of the adult and since the function of the trachea is passive during respiration, anatomic differences in the infant and adult trachea are not as apparent as they are in the larynx [1]. The infant larynx is not a miniature version of the adult larynx and there are essential differences between these two organs. The differences are related to size, location, and configuration and must be considered since the primary function of the larynx is to protect the lower airway and regulate airflow during respiration by controlling the resistance during inspiration and exhalation. The cricoid ring is the narrowest portion of the infant larynx. Although this has recently been questioned, there are insufficient data to refute the validity of this anatomic finding [2]. In the infant and child, the cricoid cartilage is a non-expansile complete ring whereas, this cartilage is open at the posterior aspect in the adult patients [3] (Fig. 6.1). In the adult patient the vocal cords are the narrowest part of the airway providing the cylindrical shape of the adult larynx in contrast to the cone shape of the pediatric larynx. This is an important distinction to make since the resistance to airflow is inversely proportional to the fourth power of the radius ($R \approx 1/\text{radius}$ [4]). One centimeter of circumferential edema in the infant larynx will decrease the cross-sectional area by 75% and increase the resistance by 16-fold as compared to the same one centimeter of edema in the adult larynx which will result in a decrease in the cross-sectional area of only 44% and threefold increase in resistance (Fig. 6.2). This becomes relevant when sedating a child with either a history of prolonged intubation in which the tracheal lumen may be narrowed or a child with a recent upper respiratory infection or croup which also may result in a circumferentially narrow airway (Figs. 6.3 and 6.4).

The larynx of the infant and young child is higher than in the adult patient. The adult larynx is located at C_{6-7} whereas, it is at C_4 in the infant and descends to the adult location as

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growth occurs during childhood. The cephalad location of the infant larynx makes oral ventilation difficult and as a result the infant is an obligate nasal breather for the first year of life [4]. The epiglottis projects vertically in the adult but posteriorly in the infant. The infant epiglottis is also narrower and omega shaped which makes it more prone to obstructing the laryngeal inlet [5] (Fig. 6.5). In the setting of nasal congestion, effective ventilation may be compromised in the unaltered state and worsened after sedation.

The tongue of the infant is larger in relation to the oral cavity than that of the older child and adult. In neonates, the tongue is more anterior than the larynx so that the epiglottis can contact the soft palate and allow respirations and sucking simultaneously. This does however predispose the infant to airway obstruction more readily than the older child. At birth, the base of the tongue resides in the oral cavity and gradually descends with the larynx to a more caudad position by the fourth year of life. The ratio of soft tissue to boney structures is higher in the infant and thus predisposes this group of patients to a greater risk of mechanical oropharyngeal obstruction. The combination of small nares, large tongue, small mandible, excess soft tissue, and short neck also increases the infant's susceptibility

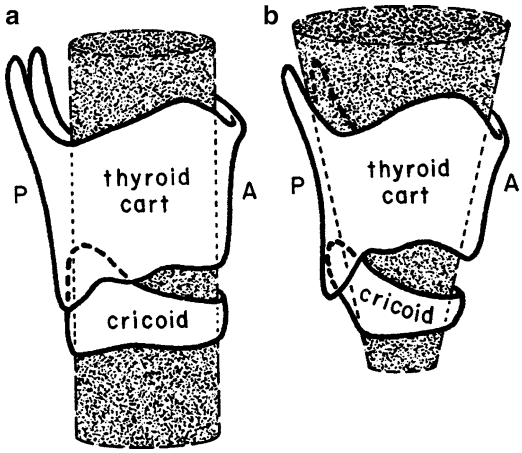

Fig. 6.1 Configuration of the adult larynx (**a**) and infant larynx (**b**). (Reprinted with permission from Wheeler et al. [22])

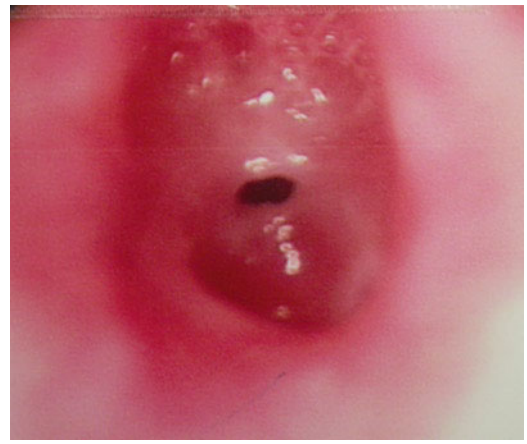

Fig. 6.3 Child with post-intubation subglottic stenosis. (Photo courtesy of Reza Rahbar, DMD, MD, Children's Hospital Boston)

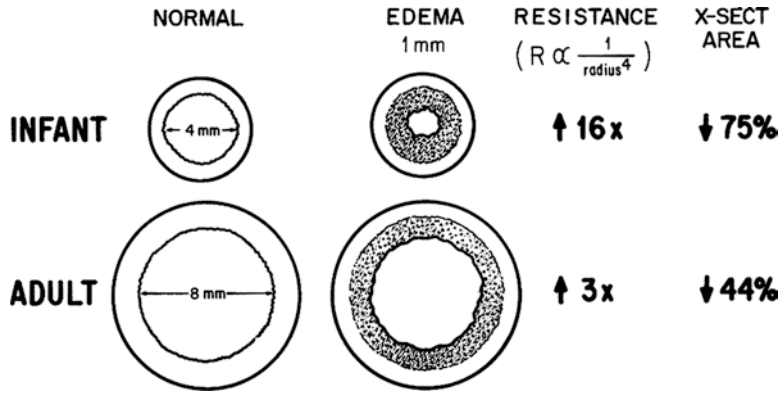

Fig. 6.2 Relative effect of circumferential edema on the infant and adult airway. (Reprinted with permission from Wheeler et al. [22])

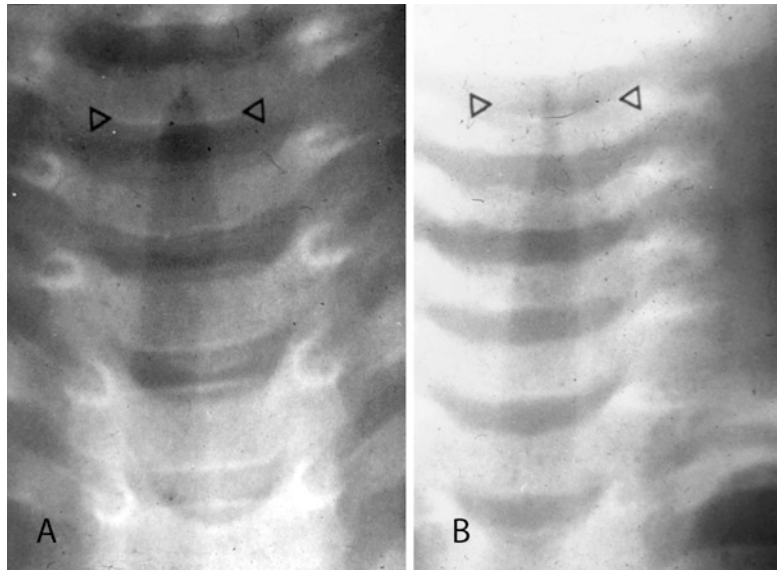

Fig. 6.4 Plain X-ray of the airway of a child with severe croup (**a**) and mild croup (**b**). Note the subglottic narrowing and appearance of the characteristics "Chrysler Building" sign. (Photo courtesy of Reza Rahbar, DMD, MD, Children's Hospital Boston)

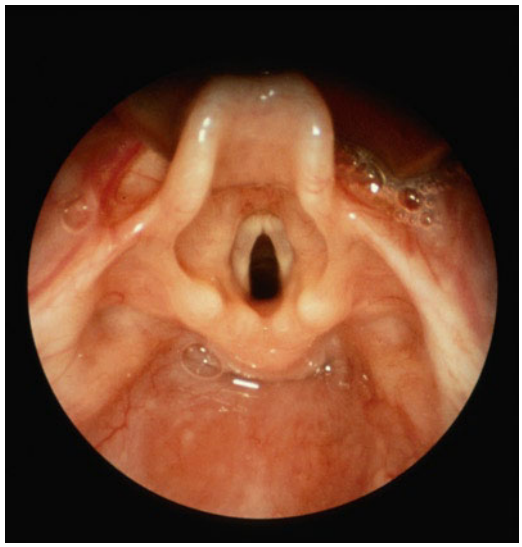

Fig. 6.5 Normal infant larynx. Note the omega shaped epiglottis. (Photo courtesy of Reza Rahbar, DMD, MD, Children's Hospital Boston)

to airway obstruction. The ribs of the infant and small child are more horizontal in orientation that those of the older child and adult and more flexible and therefore predispose the child to ventilatory compromise. As previously noted, since the metabolic rate and oxygen consumption of infants is double that of the adult and the functional residual capacity is smaller, the rapidity of desaturation in the infant and child is much greater. For this reason optimal surveillance of the airway and respiratory mechanics is essential if hypoxia is to be avoided [6].

Normal spontaneous breathing is accomplished by minimal work and obstruction of either the upper or lower airway will result in increased work of breathing. To avoid this it is essential that airway obstruction and compromises in ventilation be recognized and corrected early. Infants and children may rapidly progress from normal breathing to obstruction and compromised respiration to respiratory distress and eventual cardiac arrest. Since oxygen consumption is higher in infants, decreases in oxygen delivery will result in more rapid compromise than is observed in older patient populations. The presence of apnea leading to inadequate alveolar ventilation may rapidly progress to hypoxemia, hypercarbia, and eventual tissue hypoxia.

Assessment of the Pediatric Airway for Sedation

Physical examination reveals the general condition of a patient and the degree of the airway compromise. Laboratory examination may include assessment of hemoglobin, a chest radiograph, and barium swallow, which can aid in identifying lesions that may be compressing the trachea. Other radiologic examinations such as MRI and CT scan may be indicated in isolated instances but are not routinely ordered.

The physical examination of the airway in children begins with simple observation, since approaching an anxious child may cause inconsolable crying and distortion of the physical examination. Observation of the general appearance noting color of the skin and the presence of pallor, cyanosis, rash, jaundice, unusual markings, birthmarks, and scars from previous operations should be documented.

The degree of mouth opening should be noted and full examination on the oropharyngeal area should be completed. The distance from the temporomandibular joint to the angle of the ramus is helpful in the assessment of the adequacy of the mouth opening. The distance between the angle of the ramus to mentum is a good predictor or the ability of the mandibular boney structure to accommodate the oropharyngeal soft tissue. The presence of loose teeth should be documented. Special attention should be paid to the condition of the soft and hard palate, the dentition, and the size of the tongue. The relation of the tongue to the other oropharyngeal structures should be noted. For instance a large thick tongue may pose minimal increased risk for airway obstruction in a child with an otherwise normal oropharynx but may cause severe risk in the child with a narrow oropharynx or a high arched palate (as may be present in children with craniofacial abnormalities and syndromes) where the tongue occupies a greater proportion of the bony structure volume. The amount of the posterior pharynx that can be visualized is important and correlates with the difficulty of intubation and in sedated patients would correlate with the potential for airway obstruction. The Mallampati classification (Class I–IV) is based on the structures visualized with maximal mouth opening and tongue protrusion in the sitting position (Fig. 6.6). The soft palate, fauces, uvula, and pillars are visualized in patients with a Class I airway. The soft palate, fauces, and portion of the uvula but no pillars are visualized in Class II. The soft palate and base of uvula are visualized in Class III and only the hard palate is visualized in Class IV [7]. Tonsil size should be evaluated since the tonsils of pediatric patients are frequently enlarged and may be the source of upper airway obstruction. A standardized system for evaluation of tonsils exists and is based on the percentage of pharyngeal area that is occupied by hypertrophied tonsils. Class 0 tonsils are completely limited to the tonsillar fossa. Class +1 tonsils take

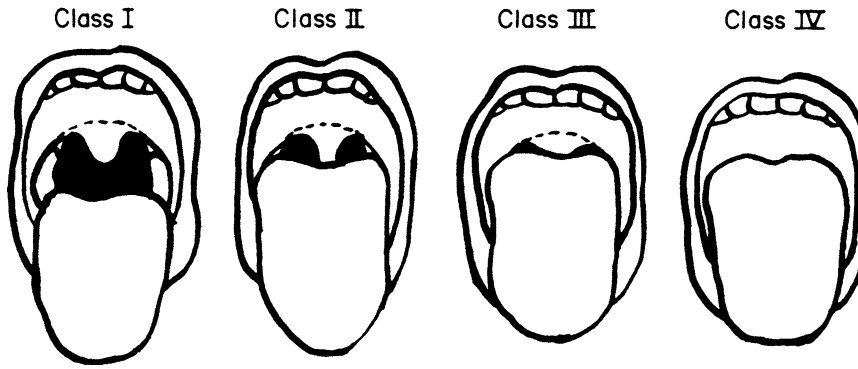

Fig. 6.6 Mallampati classification of pharyngeal structures. (Reprinted with permission from Samsoon and Young [23], Copyright Blackwell Publishing)

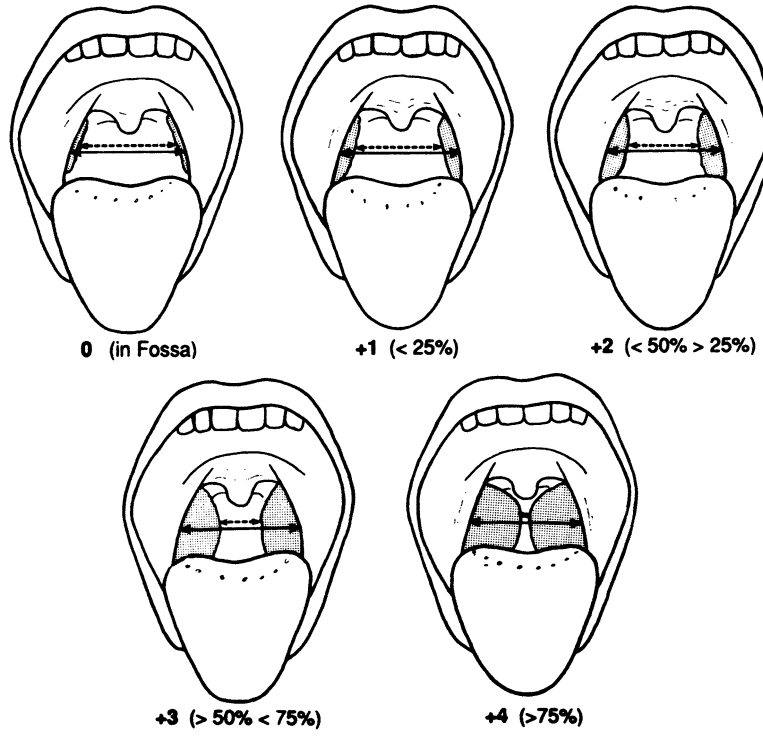

Fig. 6.7 Classification of tonsillar hypertrophy. (Reprinted with permission from Brodsky [24], Copyright Elsevier, 1989)

up less than 25%, Class +2 tonsils between 25 and 50%, and Class +3 tonsils take up 50–75% of the pharyngeal area. Class +4 tonsils take up greater that 75% of the oropharynx and are commonly referred to as "kissing tonsils" [8] (Fig. 6.7). Tonsillar hyperplasia may increase the risk of airway obstruction in the sedated patient when the tonsils occupy the oropharyngeal space outside of the tonsillar fossa as in Class +3 and Class +4 anatomy. Conversely lesser degrees of hyperplasia as seen in Class +1 and Class +2 may result in airway obstruction in the sedated patient with craniofacial abnormalities such as Down's syndrome.

Abnormal facies might be an indication of a syndrome or constellation of congenital abnormalities. One congenital anomaly often is associated with others. The neck should be examined primarily to determine if the trachea is midline and to evaluate tracheal length and soft tissue volume. In the child with a short neck and abundant soft tissue, the potential for oropharyngeal airway obstruction is greater.

The rate, depth, and quality of respirations should be evaluated. The pattern of breathing should be noted as well as the rate and depth of respiration. Use of accessory muscles may indicate an increased work of breathing due to an effort to overcome upper or lower airway obstruction. Nasal or upper respiratory obstruction is indicated by noisy or labored breathing. The color, viscosity, and quantity of nasal discharge should be documented. If the child is coughing, the origin of the cough (upper versus lower airway) and the quality (dry or wet) can be evaluated even before auscultation of the lungs. The presence of wheezing, audible stridor, or are retractions should be noted. The airway should be evaluated for ease of intubation in the case of urgent intervention. If the child will not open his or her mouth, a manual estimation of the thyrohyoid distance should be made. Children with micrognathia, as in Pierre Robin syndrome or Goldenhar's syndrome, may be especially difficult to intubate especially in an unanticipated situation.

Risk Factors for Airway Compromise or Depression

During sedation, adequate oxygenation and ventilation must be maintained despite a relative decrease in rate and depth of respiration. Any condition that causes airway compromise should be thoroughly evaluated prior to administration of sedation agents to determine if alteration in respiratory parameters will result in impaired ventilation.

During normal breathing the flow of air is laminar. As previously mentioned the resistance is inversely proportional to the fourth power of the radius. Increased airway resistance occurs when the diameter of an airway is decreased under constant pressure. The radius of an airway may be decreased by circumferential edema, external compression, mucous, secretions or bronchoconstriction. The work of breathing increases in patients with upper or lower airway disease. Increased airway resistance, decreased lung compliance, and altered central control of respiration will all affect the adequacy of respiration.

Adequacy of respiration may be based on respiratory rate, respiratory effort, tidal volume, chest auscultation, and pulse oximetry. The normal respiratory rate in infants under 1 year of age is up to thirty breaths per minute. The respiratory rate declines to 20 breaths per minute by age 8 years and equals the adult rate of 16–17 breaths per minute by age 18. Alterations in the respiratory rate can indicate underlying comorbidity such as fever, pain, acidosis, and sepsis in tachypneic patients and impending cardiovascular collapse in the bradypneic patient. Increased respiratory effort as recognized by nasal flaring, chest retractions, and uncoordinated chest excursions should alert the clinical that an increased work of breathing may increase if excessive sedation is administered.

Noisy breathing due to obstructed airflow is known as *stridor*. Inspiratory stridor results from upper airway obstruction; expiratory stridor results from lower airway obstruction; and biphasic stridor is present with midtracheal lesions. The evaluation of a patient with stridor begins with a thorough history. The age of onset suggests a cause since laryngotracheomalacia and vocal cord paralysis are usually present at or shortly after birth, whereas cysts or mass lesions develop later in life. Information indicating positions that make the stridor better or worse should be obtained, and placing a patient in a position that allows gravity to aid in reducing obstruction can be of benefit during anesthetic induction.

Patients at risk for airway compromise may have either anatomic or physiologic abnormalities which may predispose them. Anatomic abnormalities may cause the oropharyngeal or tracheobronchial airway to be compromised and ventilation be impaired by small changes in position. The anatomic imbalance between the upper airway soft tissue volume and the craniofacial size contributes to pharyngeal airway obstruction. Pharyngeal size is determined by the soft tissue volume inside the bony enclosure of the mandible. The magnitude of pharyngeal muscle contraction is controlled by neural mechanisms and the interaction between the anatomical balance and neural mechanisms, which are suppressed in sedated patients, determines pharyngeal airway size and patient ability to maintain a patent airway. An anatomic imbalance between the upper airway soft tissue volume and craniofacial size will result in obstruction. Anatomic imbalance may be compensated for by enhanced neural mechanisms which regulate pharyngeal dilator muscles in patients during wakefulness. When neural mechanisms are suppressed during sleep or sedation, relaxation of pharyngeal dilator muscles occurs and the pharyngeal airway severely narrows [9]. Small changes in function in the setting of normal anatomy may similarly cause inadequate oxygenation. Increasing the distance between the mentum and cervical column will transiently relieve the obstruction. This is achieved by positioning the patient in the sniffing position. Similarly, the sitting position displaces excessive soft tissue outside the bony enclosure through the submandibular space.

Laryngomalacia is the most common cause of stridor in infants and is usually benign and self

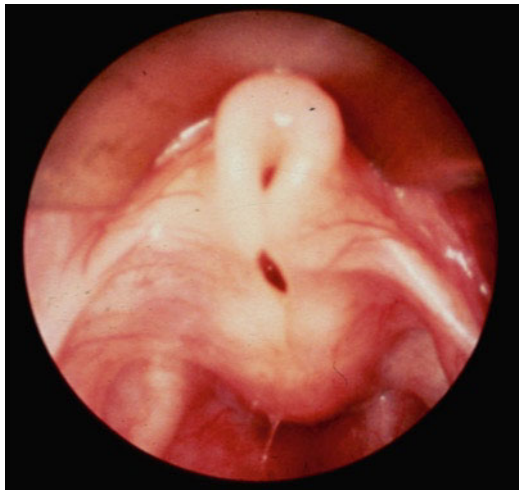

Fig. 6.8 Larynx of an infant with laryngomalacia. (Photo courtesy of Reza Rahbar, DMD, MD, Children's Hospital Boston)

limited. It occurs during inspiration and is most often due to a long epiglottis that prolapses posteriorly and prominent arytenoid cartilages with redundant aryepiglottic folds that fall into the glottis and obstruct the glottic opening during inspiration (Fig. 6.8). There is little obstruction during exhalation since the supraglottic structures are pushed out of the way during expiration. Intermittent low-pitched inspiratory stridor is the hallmark symptom which appears during the first 2 weeks of life. Symptoms peak at 6 months of age when they are at their worst then gradually resolve. Although most children are symptom free by 18–24 months, the stridor can persist for years. The definitive diagnosis is obtained by direct laryngoscopy and rigid or flexible bronchoscopy. Preliminary examination is usually carried out in the surgeon's office. A small, flexible fiberoptic bronchoscope is inserted through the nares into the oropharynx, and the movement of the vocal cords is observed [10]. Other etiologies include foreign body aspiration, infection such as croup or laryngotracheobronchitis, edema, or mass lesions such as cyst or tumor.

Grunting is a low-pitched sound that results when a patient exhales against a closed glottis and is heard on exhalation. Infants and children often grunt to keep the small airways and alveoli open in an attempt to optimize ventilation and oxygenation. The presence of grunting may be a sign of severe respiratory distress and impending respiratory failure. Underlying causes include pneumonia, acute respiratory distress syndrome, pulmonary edema, congestive heart failure, and abdominal splinting.

Wheezing during inspiration or exhalation or both indicates intrathoracic obstruction of small airways. It may be a result of intrinsic reactive airways, bronchospasm, or foreign body aspiration. Hypoxemia that is present in the wheezing patient may worsen during administration of sedation.

One of the most challenging decisions in caring for children is establishing criteria for cancelation of a procedure in the presence of an upper or lower respiratory infection. Children presenting with symptoms of uncomplicated upper respiratory infection who are afebrile, with clear secretions and appear otherwise healthy should be able to safely undergo sedation. Nasal congestion, purulent sputum production and a history of reactive airway disease are predictors of adverse respiratory events and children with these advanced symptoms of upper and potential lower respiratory disease should not undergo sedation [11].

There are many syndromes that have anatomic components related to the airway. A large tongue is associated with Down's, Hunter's, Hurler's, and Beckwith–Weidmann syndromes. Congenital hypothyroidism and Pompeii disease are also associated with a large tongue. Patients with Pierre Robin, Treacher Collins, and Goldenhar's syndrome as well as children with congenital hemifacial microsomia have micronathia, high arched palate, and a potential to have early airway obstruction when sedated. Children with tonsillar hypertrophy are at risk for mechanical airway obstruction due to large tonsils occupying a greater portion of the oropharyneal airway than normal sized tonsils.

Former premature infants are at risk for untoward respiratory events during sedation. There is a more gradual slope of the CO_2 response curve in the preterm infant which predisposes this group of patients to apnea. All neonates

exhibit periodic breathing which is manifested as interrupted ventilation by self corrected short periods of apnea without desaturation or bradycardia [12]. This tendency diminishes by 45 weeks postconceptual age. Apnea of prematurity and postanesthetic apnea are predominantly central in origin with about 10% due to mechanical obstruction. The response to airway obstruction with apnea is common in infants with periodic breathing and decreases with increasing postnatal age. In the sedated neonate and former premature infant, benign periodic breathing may evolve into frank apnea which must be managed by stimulation or assisted ventilation. To detect post-anesthetic or post-sedation apneic events, it is suggested that infants whose age is under 56 weeks postconception be monitored for 24 h after the procedure [13].

Conditions that interfere with the integrity of the laryngeal inlet or upper larynx may impair effective ventilation as a result of partial or complete airway obstruction. Upper respiratory infections cause increased secretions which may occlude the larynx in addition to the inflammatory response that can compromise the internal diameter of the laryngeal inlet. Laryngotracheobronchitis or croup also decreases the internal laryngeal diameter and produces the same clinical outcome. The incidence of epiglottitis has decreased dramatically in the past decade but may still be encountered. These patients have not only inflammation of the epiglottis but edema of the surrounding structures which severely restricts the size of the larynx and encroaches on the area for ventilation to occur.

Patients who have sustained airway trauma or thermal injury should be considered in this category as well. Children who have experienced prolonged intubation may have decreased laryngeal inlet diameter as a result of fibrosis from congenital or acquired subglottic stenosis (Figs. 6.9 and 6.10). Any agent that will decrease the pharyngeal muscle tone and rate and depth of respiration in this setting should be given with extreme caution and warrants vigilance. Other conditions that restrict the laryngeal inlet are subglottic stenosis, laryngeal cysts, and papillomatosis.

There is a similar concern for narrowing and compromise of the larynx from external factors. Goiter or other tumors of the neck that are extrinsic to the larynx may cause compression and functional restriction to ventilation. Children with arthrogryposis or congenital abnormalities in which the neck is fused may have difficulty with positioning and subsequent ventilation when airway function is depressed during sedation.

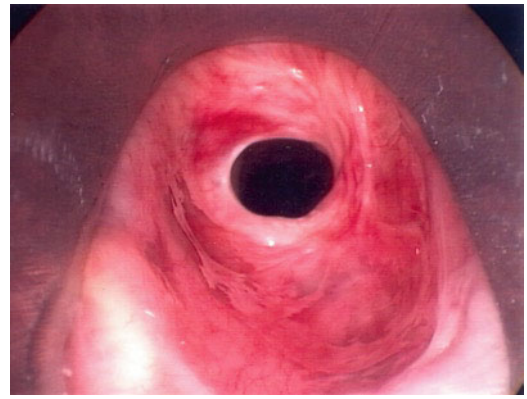

Fig. 6.9 Larynx of an infant with congenital subglottic stenosis. (Photo courtesy of Reza Rahbar, DMD, MD, Children's Hospital Boston)

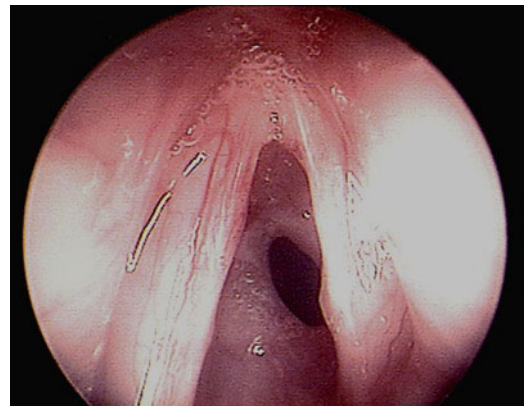

Fig. 6.10 Larynx of an infant with acquired post-intubation subglottic stenosis. (Photo courtesy of Reza Rahbar, DMD, MD, Children's Hospital Boston)

Children with an anterior mediastinal mass are at significant risk for airway compromise during sedation due to compression of the intrathoracic larynx (Figs. 6.11 and 6.12). Although lymphomas constitute the largest group of masses that arise in the anterior mediastinum, other masses that may present in this location include teratomas, cystic hygromas, thymomas, hemangiomas, sarcomas, desmoid tumors, pericardial cysts, and diaphragmatic hernias of the Morgagni type.

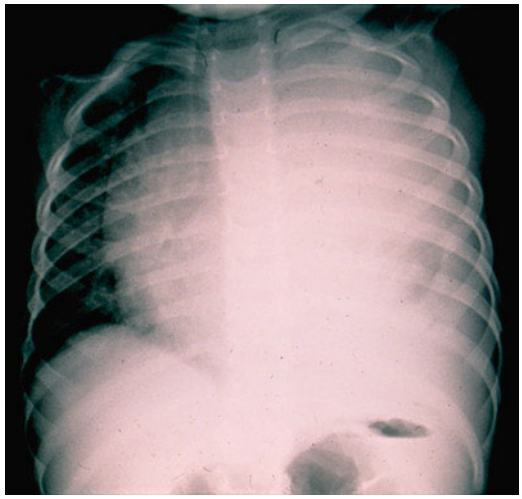

Fig. 6.11 A 20-month-old male with a large anterior mediastinal mass

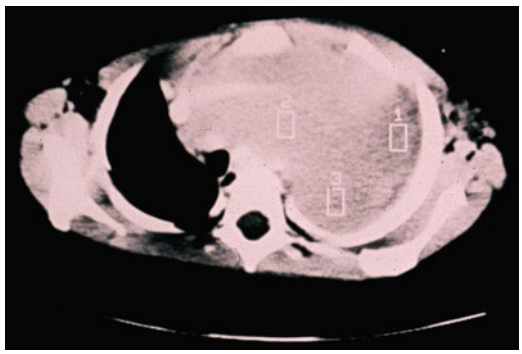

Fig. 6.12 CT scan illustrating a large anterior mediastinal mass compressing the lung and causing tracheal deviation

To understand the pathophysiology of the anterior mediastinum, it is important to be familiar with the anatomy. The mediastinum is defined as the extrapleural space in the thorax that is bounded anteriorly by the sternum, posteriorly by the thoracic vertebrae, superiorly by the thoracic inlet, and inferiorly by the diaphragm. Structures contained within the mediastinum that may undergo compression from an enlarging mass are the trachea and the mainstem bronchi, superior vena cava, aortic arch, main pulmonary artery, and a portion of the heart itself.

Patients with anterior mediastinal masses may present with varied signs and symptoms referable to both the cardiovascular and respiratory systems and are directly related to the location and size of the mass, as well as the degree of compression of surrounding structures. The most commonly observed respiratory symptom is cough, especially in the supine position, which results from anterior compression of the trachea. Infants less than 2 years of age are more likely to experience wheezing as a sign of tracheal compression, whereas children older than 2 years of age usually present with malaise, cough, fever, and a neck mass. Other respiratory findings in patients of all ages include tachypnea, dyspnea, stridor, retractions, decreased breath sounds, and cyanosis on crying, all of which should alert the practitioner to some degree of airway compromise that may worsen when positive intrathoracic pressure is generated.

Cardiovascular symptoms result from compression of the aortic and pulmonary vessels, as well as the right atrium and right ventricle. This can lead to both hypotension secondary to inadequate cardiac filling and restricted pulmonary blood flow resulting in poor oxygenation despite adequate ventilation. Findings referable to the cardiovascular system include fatigue, headache, hypotension or pallor in the supine position, a feeling of light-headedness, superior vena cava syndrome (facial edema, cyanosis, jugular venous distension), and the appearance of a new murmur, especially in the area of the pulmonary valve. It is essential that the practitioner search for these signs and symptoms when interviewing and examining patients with mediastinal masses in an attempt to ascertain the degree of respiratory and cardiovascular compromise present. Patients with minimal symptoms can have catastrophic events if subtle indicators are overlooked. Improvement of these physiologic changes is often quickly achieved by moving the patient into a sitting or left lateral position.

Sleep Disordered Breathing

Sleep disordered breathing (SDB) is a spectrum of disorders ranging from primary snoring to obstructive sleep apnea syndrome (OSAS). The mildest form of SDB is primary snoring which is noisy breathing without clinical manifestations and occurs in 20% of normal children [14].

Although SDB affects 10% of the population only 1–4% will progress to OSAS. OSAS is characterized by periodic, partial, or complete obstruction of the upper airway during sleep. Airway obstruction is characterized by an anatomic imbalance between the upper airway soft tissue volume and craniofacial size. Suppression of pharyngeal dilator muscles during sleep and anesthesia occur in the patient with obstructive sleep apnea as opposed to patients who are just noisy breathers or have mild to moderate snoring.

Repetitive arousal from sleep to restore airway patency is a common feature as are episodic sleep-associated oxygen desaturation, hypercarbia, and cardiac dysfunction as a result of airway obstruction. Individuals who experience obstruction during sleep may have snoring loud enough to be heard through closed doors or observed pauses in breathing during sleep. They may awaken from sleep with a choking sensation. Parents report restless sleep in affected children and frequent somnolence or fatigue while awake despite adequate sleep hours. These children fall asleep easily in non-stimulating environments and are difficult to arouse at usual awakening time. Type 1 OSAS is characterized by lymphoid hyperplasia without obesity whereas type 2 OSAS patients are obese with minimal lymphoid hyperplasia. Approximately, ten percent of OSAS is present in preschool and school aged children and is thought to decline after 9 years of age [15].

Obesity changes craniofacial anthropometric characteristics therefore body mass index of 95% for age or greater is a predisposing physical characteristic that increases the risk of developing OSAS. Children with craniofacial abnormalities including a small maxilla and mandible, large tongue for given mandibular size and thick neck have a similar increased risk. Many of these children have syndromes which are associated with additional comorbidities. Anatomic nasal obstruction and Class IV touching tonsils reduce oropharyngeal cross-sectional area which constitutes an addition risk. Pharyngeal size is determined by the soft tissue volume inside the bony enclosure of the mandible and an anatomic imbalance between the upper airway soft tissue volume and craniofacial size will result in obstruction. The magnitude of pharyngeal muscle contraction is controlled by neural mechanisms and the interaction between the anatomical balance and neural mechanisms determines pharyngeal airway size. Increased neural mechanisms can compensate the anatomical imbalance in obstructive sleep apnea patients during wakefulness. When the neural mechanisms are suppressed during sleep or anesthesia resulting in no suppression of pharyngeal dilator muscles (as is present in non-OSAS patients), the pharyngeal airway severely narrows because of the anatomical imbalance. Increasing bony enclosure size will provide relief of airway obstruction. This is only accomplished surgically by mandibular advancement. Increasing the distance between the mentum and cervical column by positioning will transiently relieve the obstruction as long as the sniffing position is maintained. Similarly, the sitting position displaces excessive soft tissue outside the bony enclosure through the submandibular space.

The long-term effects of OSAS are not limited to the airway. These children have other systemic comorbidities. Increased body mass index and obesity may lead to increased cognitive vulnerability as illustrated by the increased frequency of hyperactivity and increased levels of C-reactive protein. The duration of OSA has no relation to reversibility of neurobehavioral impairment since many believe that episodic hypoxia alters the neurochemical substrate of the prefrontal cortex causing neuronal cell loss. Metabolic syndrome consists of insulin resistance, dyslipidemia, and hypertension. It is felt that OSAS is a risk factor for metabolic syndrome in obese children but not in nonobese patients. Cardiovascular and hemodynamic comorbidities are more common in OSAS patients. These consist of altered regulation of blood pressure as well as alterations in sympathetic activity and reactivity. Also present are endothelial dysfunction and initiation and propagation of inflammatory response facilitated by increases in levels of C-reactive protein. Systemic inflammation using interleukins as a marker is a component of OSAS in both obese and nonobese children and is reversed after tonsillectomy. Systemic hypertension, changes in left ventricular geometry and intermittent hypoxia

leading to pulmonary artery hypertension are well-described comorbidities present in patients with OSAS.

The mainstay of the management is surgical removal of tonsils and adenoids which carries an 85% success rate in resolving OSAS. Recurrence may occur in children with craniofacial abnormalities and in others and if surgical intervention does not resolve the problem, CPAP at night is the next treatment modality. Many of these children however may present for imaging or require sedation prior to removal of the tonsils or adenoids.

For patients undergoing sedation, the preoperative evaluation begins with the history. Questions to ask parents include the presence of difficulty breathing during sleep, apnea during sleep, sweating during sleep, restless sleep or behavioral problems, and/or somnolence during the day. A positive finding of any of the above characteristics should alert the practitioner to the possibility of some degree of OSAS [16]. Specific attention should be paid to the frequency of tonsillar infection, recent upper respiratory infections, SDB, and cardiovascular abnormalities. The physical exam should include observation of audible respiration, mouth breathing, nasal quality to speech, chest retractions, long facies, retrognathic mandible, and inspection of tonsillar size. Auscultation should be specifically directed to detect wheezing and stridor. Polysomnography (PSG), otherwise known as the sleep study, is the gold standard for diagnosis of OSAS. A sleep study is suggested to direct the postoperative or postprocedural disposition. It is essential in patients with comorbidities and high risk features such as morbid obesity, craniofacial abnormalities, neuromuscular disorders, cor pulmonale, systemic hypertension, difficulty breathing during sleep growth impairment due to chronic obstructed breathing, and a history of severe prematurity [17]. Obesity changes craniofacial anthropometric characteristics and a body mass index of 95% for age or greater is a risk factor for OSA which should be quantified by PSG. Craniofacial abnormalities which specifically include small maxilla and mandible, large tongue for given mandible size, and thick neck similarly should be evaluated by sleep study. Despite this, most patients do not have this examination prior to surgery. It is expensive, time consuming, and unavailable in some medical centers. The nadir of oxygen saturation and respiratory disturbance index (RDI), which is the number of apneic episodes per hour, are measured during PSG. Apnea is defined as decreased in flow greater than 90% for two breaths or more. Hypopnea is defined as decreases in air flow greater than 50% coupled with 3% decrease in oxygen saturation or EEG arousal. A RDI of two or more is necessary for the diagnosis of OSAS. Mild OSAS is defined as RDI of 5–10 events, moderate 10–20 events, and severe 20–30 events.

When sedation without a secured airway is planned it is imperative that the level of consciousness, adequacy of ventilation, and oxygenation be continuously monitored and the risk of apnea be evaluated. Patients exposed to recurrent hypoxia exhibit an altered response to narcotics which is manifested by decreases in minute ventilation, respiratory frequency, and tidal volume. It is therefore suggested that no sedative premedication be administered to OSAS patients prior to a general anesthetic and narcotics be administered in incremental doses beginning with one half the recommended dose, until adequacy of ventilation and respiration is determined. Patients with OSAS who are given the same dose of narcotic as non-OSAS patients have a very high risk of serious respiratory compromise. [18, 19] Similarly, patients should not be discharged until fully awake and breathing at a baseline rate and depth. The supraglottic obstruction secondary to decreased muscle tone may contribute to desaturation. Children who have increased severity of OSAS, low weight, and age under 3 years exhibit a higher rate of complications. They are more likely to require supplemental oxygen, the use of an oral airway, and require assisted ventilation. Slow return of upper airway tone may lead to desaturation and laryngospasm on emergence especially in those patients who are known to have a RDI greater than 30.

There is no agreement on the specific criteria that preselect elective OSAS patient for admission and monitoring postprocedure [20].

Inclusive characteristics may include the following: PSG proven OSAS with RDI >40, RDI >20 plus either desaturation <70%, or age less than 3 years, or weight <3% for age. Children with craniofacial syndromes or neuromuscular disease are included as children with complex or cyanotic cardiac disease. Additional indications include morbid obesity, known cor pulmonary and pulmonary hypertension and preexisting asthma or other unrelated respiratory comorbidities.

Identification and Treatment of Airway Related Adverse Events

The best way to minimize airway and respiratory compromise is to optimize the situation and prevent it. When a child is sedated, the best prevention is to insure that the position provides the best anatomic orientation for airway patency. The patient should be in the supine position with the head in a sniffing position and shoulders slightly elevated. This requires that the protrusion of the occiput is balanced by slight shoulder elevation to prevent neck flexion and airway compromise (Fig. 6.13). Supplemental oxygen should be administered by nasal prongs, mask, or blow-by to keep oxygen saturation above 95%.

If, despite proper positioning, the airway becomes obstructed and ventilation is compromised, an oropharyngeal or nasopharyngeal airway may be placed. Both of these devices improve ventilation by maximizing the space for gas entry between the tongue and posterior pharynx. The appropriate size must be chosen to prevent worsening of the obstruction or irritation of the larynx resulting in laryngospasm (Fig. 6.14). The appropriate oropharyngeal airway size may be determined by measuring the distance between the lips and the angle of the mandible. If the airway is too large the tip may rest on the epiglottis and cause laryngeal irritation and spasm. If the airway is too small it may compress the tongue and cause it to move posteriorly thus causing worsening of the oropharyngeal obstruction. The proper nasopharyngeal size may be estimated by measuring the distance between the nares to the angle of the mandible. Extreme caution must be used when placing a nasopharyngeal airway in a toddler or young child due to the presence of hypertrophied adenoid tissue which can bleed profusely when dislodged [21]. If airway patency is not restored with repositioning of the head and shoulders despite the use of an artificial airway, the jaw thrust may be useful. This maneuver increases the distance between the base of the tongue and the vocal cords and helps to provide the maximum area for air exchange. In addition, positioning the patient on his/her side with the mouth opened may also relieve obstruction.

If it is determined that ventilation must be assisted to maintain oxygenation then bag-mask ventilation may be instituted. The laryngeal mask airway (LMA) may also be a useful adjunct if the

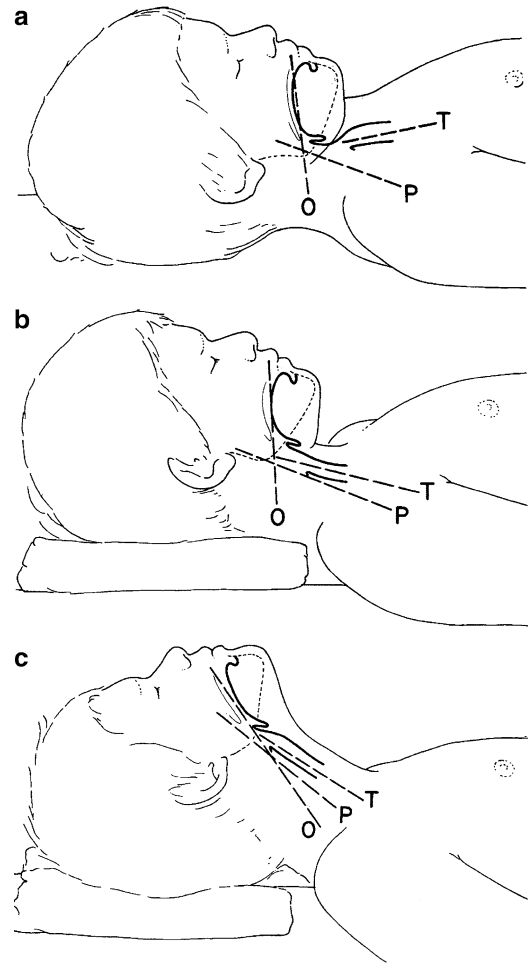

Fig. 6.13 Alignment of oral, pharyngeal, and tracheal axis variation with head position. (Reprinted with permission from Wheeler et al. [22])

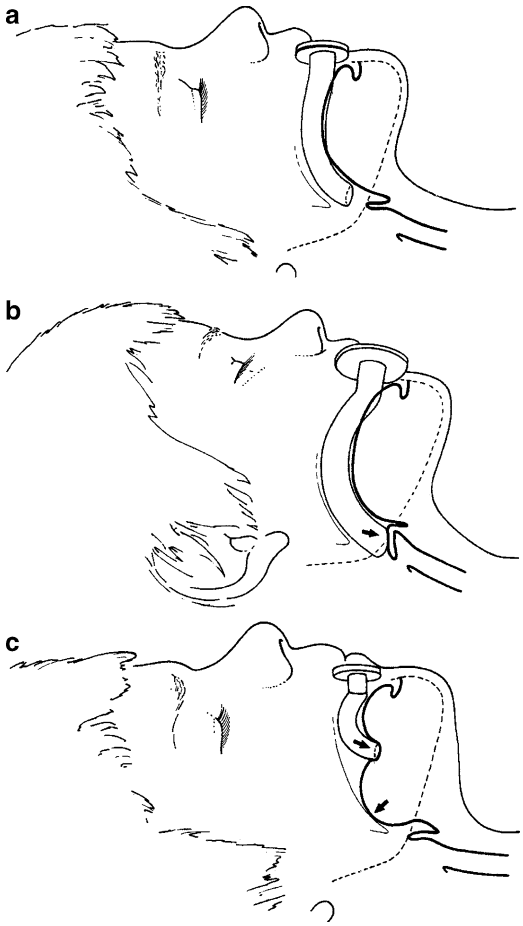

Fig. 6.14 Effects of different size oropharyngeal airway placement. (Reprinted with permission from Wheeler et al. [22])

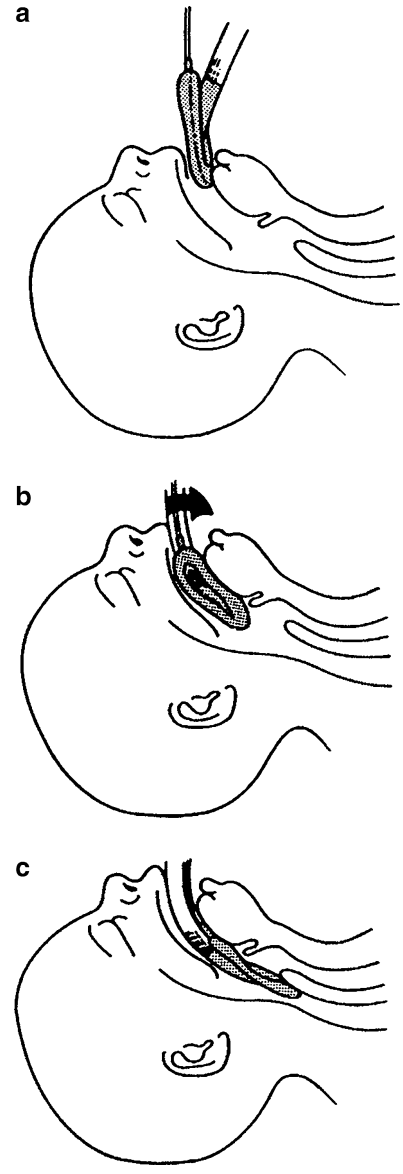

Fig. 6.15 Technique of laryngeal mask insertion in infants and children. (Reprinted with permission from Haynes and Morton [25], Copyright Blackwell Publishing)

patient has progressed beyond spontaneous ventilation and requires assisted or controlled ventilation. The LMA is an appropriate intermediate step to maintain an airway that does not require endotracheal intubation. The LMA is inserted without the need to visualize the vocal cords and forms an airtight seal around the glottis rather than plugging the pharynx. This positioning provides both a patent path for gas entry during positive-pressure ventilation and simultaneously prevents the supralaryngeal structures from encroaching on the glottis. The vocal cords move freely during respiration and are not manipulated, thus avoiding a potent stimulus for laryngospasm. The ideal patient position for insertion is the supine sniffing position but it can be inserted in the neutral position as well. In infants and young children, the epiglottis is prominent and may provide a mechanical barrier to successful placement. To overcome this, it is recommended that the LMA be place with the vented side facing the palate and advanced while turning in an attempt to flick the epiglottis out of the way (Fig. 6.15). Assisted spontaneous ventilation may be carried out in this manner. If undisturbed, the LMA provokes very little stimulus and can be left in place

until the patient's protective reflexes have returned and respirations resume spontaneously. If ventilation cannot be achieved, endotracheal intubation with controlled ventilation may have to be instituted.

Summary

Sedation of children for diagnostic or therapeutic procedures is often an alternative to general anesthesia due to the common belief that it carries less risk and requires fewer resources. Although this is not a completely erroneous perspective, sedation is not without risks. A thorough understanding of the pediatric airway anatomy at each developmental stage is essential as well as the physiologic consequences that occur when consciousness is altered. Appropriate monitoring must be utilized and personnel who are knowledgeable with regard to the potential adverse events and skills to treat them must be immediately available. When these conditions are met, sedation of infants and children is a reasonable and safe practice.

Case Studies

Case 1: Obstructive Sleep Apnea

A 5-year-old boy with osteomyelitis Class 4 tonsillar hyperplasia presents to the interventional radiology suite for insertion of a peripherally inserted central catheter (PICC) for antibiotic administration. Attempts at PICC insertion were unsuccessful due to patient movement and difficulty in locating an appropriate vessel. The mother reports that the child is otherwise healthy except that he seems to choke when he is asleep and sometimes awakens startled in the middle of the night. He is overweight for his age and has some difficulty concentrating and sitting still in school. His physical exam reveals as a moderately overweight boy with a short neck and nasal breathing. His oropharyngeal examination is positive for Class 4 kissing tonsils which occupy greater that 75% of the oropharyngeal volume and a Mallampati Class 3 classification for intubation. He is taking no medications and has not had a sleep study.

The considerations for this child would be appropriateness for sedation, choice of monitoring required, and postprocedural disposition. This is a child in whom a sleep study would be desirable but in the absence of this information it may be assumed that he is at risk for OSAS based on his weight, short neck, and large tonsils. He may undergo sedation but is at risk for airway obstruction and desaturation, thus he must be monitored in the presence of a practitioner who has airway management skills should this occur. Monitors should include EKG, pulse oximeter, capnography, and blood pressure measurements. Supplemental oxygen should be administered by nasal cannula. Some head-up position should be maintained as much as possible to facilitate diaphragmatic excursion. Agents that maintain spontaneous respirations and do not produce significant respiratory depression should be considered. Due to the probability of OSAS, this patient should be admitted to the hospital overnight for observation. The inclusion criteria for overnight admission include obesity, Class 4 tonsils as well as a history consistent with significant SDB and probable OSAS. Alternatively, if the child underwent tonsillectomy and adenoidectomy in advance of sedation, the radiologic study could be scheduled 2–3 weeks postoperatively. Waiting this amount of time insures that the hypopharynx was well healed. In this case if a repeat sleep study was repeated and improved, the post-sedation admission might be eliminated; however, in the absence of a

repeat sleep study the overnight post-sedation admission still is required.

Case 2: Anterior Mediastinal Mass

An otherwise healthy 14-year-old male presented to his pediatrician with a history of new onset cough and difficulty sleeping. The only significant findings on physical exam were shortness of breath when lying down, some jugular venous distention in the supine position, and a single enlarged cervical lymph node. Breath sounds were diminished bilaterally but more on the left side. The child was sent to the hospital for a chest X-ray and a large anterior mediastinal mass was noted. An MRI for further classification was requested.

Patients with an anterior mediastinal mass may present with varied signs and symptoms referable to both the cardiovascular and respiratory systems. Symptoms are directly related to the location and size of the mass, as well as the degree of compression of surrounding structures. The most commonly observed respiratory symptom is cough, especially in the supine position, which results from anterior compression of the trachea by a mass located in the anterior mediastinum. Infants less than 2 years of age are more likely to experience wheezing as a sign of tracheal compression, whereas children older than 2 years of age usually present with malaise, cough, fever, and a neck mass. Other respiratory findings in patients of all ages include tachypnea, dyspnea, stridor, retractions, decreased breath sounds, and cyanosis on crying, all of which should alert the anesthesiologist to some degree of airway compromise that may worsen when positive intrathoracic pressure is generated.

Cardiovascular symptoms result from compression of the aortic and pulmonary vessels, as well as the right atrium and right ventricle. This can lead to both hypotension secondary to inadequate cardiac filling and restricted pulmonary blood flow resulting in poor oxygenation despite adequate ventilation. Findings referable to the cardiovascular system include fatigue, headache, hypotension or pallor in the supine position, a feeling of light-headedness, superior vena cava syndrome (facial edema, cyanosis, jugular venous distension), and the appearance of a new murmur, especially in the area of the pulmonary valve. It is essential that the clinician search for these signs and symptoms when interviewing and examining patients with mediastinal masses in an attempt to ascertain the degree of respiratory and cardiovascular compromise present. Patients with minimal symptoms can have catastrophic events when sedated if subtle indicators are overlooked.

Sedation is best accomplished with the child in the semi-Fowler or full sitting position since the supine position leads to decreased expansion of the rib cage and cephalad displacement of the diaphragm. Patients who are asymptomatic while awake may exhibit airway obstruction during sedation in the supine position, which is explained by a reduction in the dimensions of the thorax that limits the available space for the trachea relative to the tumor. The increase in central blood volume that accompanies the supine position can also lead to increased tumor volume and size, thus contributing to the potential for airway obstruction. The patient should breathe spontaneously and small dose of sedative agents may be administered as the patient is lowered into position. Agents that suppress respirations should be avoided. The adequacy of ventilation and blood pressure should be checked at frequent intervals until the optimum surgical position has been achieved. If at any time a decrease in blood pressure occurs and causes an inability to oxygenate despite adequate ventilation or if an inability to provide adequate ventilation is encountered, the patient should be returned to the upright or lateral position. This will generally relieve airway obstruction caused by the tumor mass.

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Pediatric Physiology: How Does it Differ from Adults?

7

Dean B. Andropoulos

Introduction

Safe sedation of pediatric patients requires a thorough understanding of the physiological differences between infants, children, adolescents, and adults. Especially in small infants, there is much less margin for any errors in diagnosis and treatment of respiratory or cardiovascular depression during sedation procedures. This chapter will review developmental aspects of respiratory, cardiovascular, central nervous system, renal, hepatic, hematologic, and temperature homeostatic systems, highlighting the differences between children and adults and emphasizing their relevance to sedation procedures in children.

Respiratory Physiology

Many physiologic differences in respiratory physiology between children and adults can be understood by anatomical differences in the airway and lungs [1]. The major anatomical airway differences include the tongue, where the infant's tongue is relatively large compared to the adult, and more prone to airway obstruction. The larynx of the infant is more cephalad, lying at the C3–4 level, versus the adult position of C4–5. The infant epiglottis is narrow and omega-shaped, versus the flat, broad, U-shaped epiglottis of the adult. The cricoid ring is the narrowest portion of the infant and child up to about 4–6 years of age; thereafter the glottic opening itself is the narrowest portion of the airway. In terms of the intrathoracic airways, they are fully formed, including the terminal bronchioles, relatively early in gestation. However, alveolar number and development are incomplete at birth, with the full term infant having 20–50 million terminal airspaces, which are immature alveoli. Lung development occurs rapidly with nearly the adult number of 300 million or more alveoli reached by 3 years of age [2]. Early in postnatal life the lung volume of the neonate and young infant is disproportionately small in relation to body size, the functional residual capacity (FRC) is only about 25 mL/kg in contrast to 40–50 mL/kg in the older child and adolescent. In addition, metabolic rate and therefore oxygen requirement in mL/kg/min is 2–3 times higher in the neonate compared to the adult.

Lung and chest wall mechanics are very different in the neonate and young infant, compared to the older child and adult [2, 3]. The soft and compliant thoracic cage means that the outward recoil of the thorax is very low in the neonate, and this means that resting negative thoracic pressure in

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infants is low. Neonates depend on the diaphragm for the power to produce lung expansion to a much greater degree than the older child. In addition, since airway resistance is proportional to the inverse of the fourth power of the radius of the airway, the much smaller airways of infants and young children experience a significant increase in resistance when partially obstructed by edema, inflammation, bronchospasm, or secretions. The low FRC, small airways, and poor elastic recoil of the thorax in neonates makes the small airways vulnerable to airway closure, and thus hypoventilation and hypoxemia can occur quickly in the sedated infant who is not crying or taking deep breaths [4]. Figure 7.1 displays the difference in lung volumes between the neonate and adult [5], and Table 7.1 summarizes the developmental changes in respiratory physiology from birth through adulthood.

Fetal hemoglobin predominates in the neonate and young infant, and this causes another important difference in respiratory physiology from the older child and adult. The oxyhemoglobin dissociation curve is shifted to the left in neonates because of fetal hemoglobin, meaning that the partial pressure of oxygen necessary to produce an oxyhemoglobin saturation of 50% (the P_{50}) is only 19 mmHg, versus 27 mmHg with mature adult hemoglobin A [6] (Fig. 7.2). This is an adaptation to fetal life, where oxygen tensions are low, and with hemoglobin F loading the hemoglobin with oxygen molecules is facilitated; however unloading of oxygen to the tissues is more difficult with a left-shifted curve. Therefore in the neonate and young infant, a given oxygen tension will produce a higher oxygen saturation, but this extra reserve is required to provide additional oxygen to unload to the tissues. Adult hemoglobin A predominates by 6 months of age.

Pulse oximetry is the standard for monitoring of oxygenation during all sedation procedures. Pulse oximeter arterial saturation (SpO_2) is a very useful monitor, generally accurate to ±2% when compared to arterial blood oxygen saturation measured by co-oximetry. In a child without cardiac or pulmonary disease, normal SpO_2 is 96–100% on room air and unsedated. Sedative medications often cause a degree of hypoventilation, both in slowing respiratory rate, and decreasing tidal volumes and FRC. Upper airway obstruction is also common, which may interfere with oxygenation. These factors make it necessary to deliver supplemental oxygen to virtually all patients undergoing sedation procedures, either by nasal cannula or face-mask, to enable SpO_2 to remain in the normal 96–100% range. A decrease of 5% or less from baseline, as long as the patient is otherwise stable without significant respiratory depression or upper airway obstruction, is common and can usually be treated with increased supplemental oxygen. A decrease of 10% or more from baseline is cause for urgent intervention to detect and treat upper airway obstruction or hypoventilation, the two most common causes of arterial desaturation during sedation. Children with cyanotic congenital heart disease may have resting awake SpO_2 ranging from 70–95%, and it is important to understand the anatomy, pathophysiology, and normal baseline saturations before proceeding with sedation in these patients. The general guideline that a 5% decrease in SpO_2 from baseline is common and may be treated with additional supplemental oxygen, and that a 10% decrease is a cause for urgent intervention, applies to the congenital heart disease population as well. Other patients with chronic lung diseases, i.e., bronchopulmonary dysplasia (BPD) or cystic fibrosis, may also have decreased baseline SpO_2, often ranging from 85 to 95%.

Monitoring of respiration also often includes end-tidal CO_2, which can easily be monitored using a special or modified nasal cannula. Although dilution of the exhaled gas with inspired oxygen, poor fit of nasal cannula, increased dead-space ventilation, or right to left intracardiac shunting often increases the gap between arterial blood $PaCO_2$, and end-tidal CO_2, it is a very sensitive monitor of airway obstruction, and an accurate method to measure respiratory rate. In addition, low cardiac output states or cardiac arrest are accompanied by a sudden decrease or absence of end-tidal CO_2.

Common conditions in pediatric patients which reduce respiratory reserve even further include BPD in former premature infants who suffered from respiratory distress syndrome (RDS) [7]. BPD is defined as a chronic condition of fibrosis and loss of alveoli in the lung following RDS with a requirement for supplemental oxygen beyond

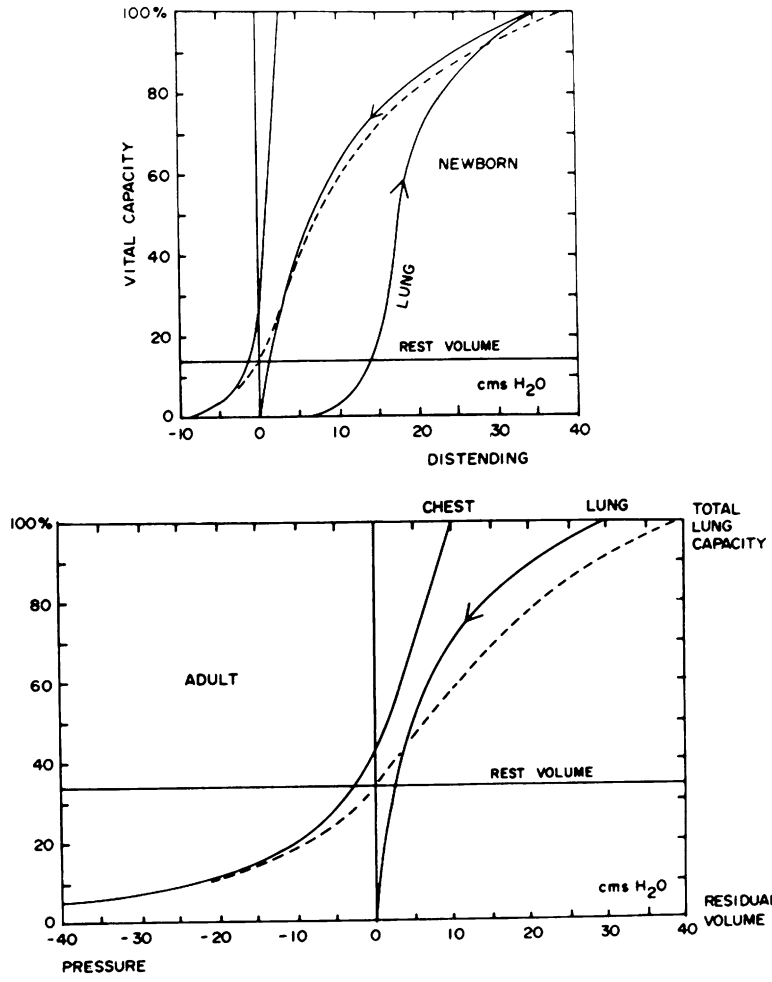

Fig. 7.1 Pressure–volume curves of the infant and adult respiratory systems. The rest volume is the volume at zero intrathoracic pressure, where the outward recoil of the chest wall is equal to the inward elastic recoil of the lungs. In the neonate, this volume is very low (10–15% of total lung capacity) compared to the adult, and is just above the FRC and often below the closing volume of the small airways. In the adult this value is much higher at 30–35% of the total lung capacity. During sedation, where quiet breathing or respiratory depression may occur, the neonate and small infant is much more prone to airway closure, resulting in intrapulmonary shunting and hypoxemia. (Reproduced with permission from Smith and Nelson [5])

30 days of life. These infants may present for sedation months or years later, and even though they have apparently recovered, pulmonary reserve is often considerably limited. Other common chronic conditions include asthma or reactive airways disease, affecting an estimated six million children in the United States [8]. Pre-sedation assessment must always include questioning about asthma and a thorough airway and pulmonary examination; elective sedation in the face of an asthma exacerbation is contraindicated. Children also have frequent upper respiratory infections, which predispose them to increased airway complications during a sedation procedure. Elective sedation procedures should be performed in children with upper respiratory tract infections only after a thorough risk-benefit assessment.

All of the factors reviewed earlier make the small infant in particular vulnerable to rapid onset of hypoxemia and hypercarbia if sedated too deeply, and the practitioner must be vigilant especially when sedating infants. Supplemental

Table 7.1 Age dependent respiratory variables

Variable	Units	Neonate	6 months	12 months	3 years	5 years	9 years	12 years	Adult
Approx. weight	kg	3	7	10	15	19	30	50	70
Respiratory rate	Breaths/min	50 ± 10	30 ± 5	24 ± 6	24 ± 6	23 ± 5	20 ± 5	18 ± 5	12 ± 3
Tidal volume	mL	21	45	78	112	170	230	480	575
	mL/kg	6–8	6–8	6–8	6–8	7–8	7–8	7–8	6–7
Minute ventilation	mL/min	1,050	1,350	1,780	2,460	4,000		6,200	6,400
	mL/kg/min	350	193	178	164	210		124	91
Alveolar ventilation	mL/min	665		1,245	1760	1,800		3,000	3,100
	mL/kg/min	222		125	117	95		60	44
Dead space/tidal volume ratio		0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Oxygen consumption	mL/kg/min	6–8							3–4
Vital capacity	mL	120			870	1,160		3,100	4,000
	mL/kg	40			58	61		62	57
Functional residual capacity	mL	80			490	680		1,970	3,000
	mL/kg	27			33	36		39	43
Total lung capacity	mL	160			1,100	1,500		4,000	6,000
	mL/kg	53			73	79		80	86
Closing volume as a % of vital capacity	%					20		8	4
No. of alveoli	Saccules × 10^6	30	112	129	257	280			300
Specific compliance	C_L/FRC:mL/cm H_2O/L	0.04	0.038			0.06			0.05
Specific conductance of small airways	Ml/sec/cm H_2O/g	0.02		3.1	1.7	1.2		8.2	13.4
Hematocrit	%	55 ± 7	37 ± 3	35 ± 2.5	40 ± 3	40 ± 2	40 ± 2	42 ± 2	43–48
Arterial pH	pH units	7.30–7.40		7.35–7.45					7.35–7.45
$PaCO_2$	mmHg	30–35		30–40					30–40
PaO_2	mmHg	60–90		80–100					80–100

Source: Adapted and reproduced with permission from O'Rourke and Crone [2]

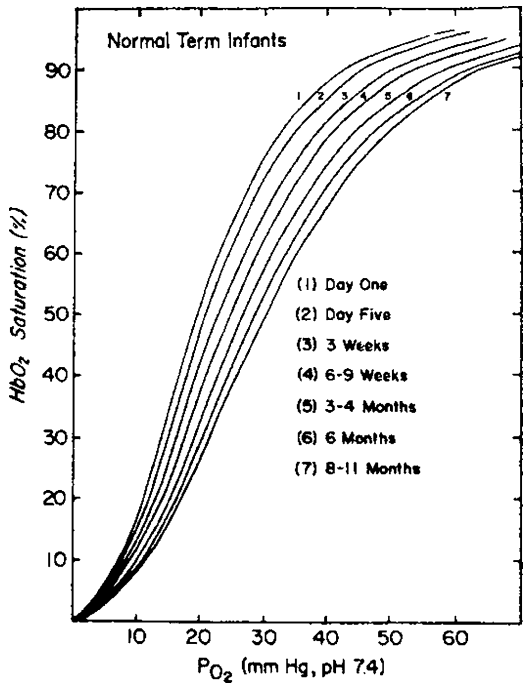

Fig. 7.2 Comparison of oxyhemoglobin dissociation curves from blood of infants at different ages. At birth the P50 is 19 mmHg, and by 8 months of age has shifted to the right and is 27 mmHg, a result of the change from predominately fetal hemoglobin F to adult hemoglobin A. (Reproduced with permission from Delivoria-Papadopoulos et al. [6])

oxygen should be used in almost every setting in which infants and children are sedated; the only exceptions being in premature neonates where retinopathy of prematurity may be a risk, and in relatively uncommon congenital heart defects in neonates with a single functional ventricle, such as hypoplastic left heart syndrome.

Cardiovascular Physiology

Development from Neonate to Older Infant and Child

At birth the neonatal heart must suddenly change from a parallel circulation to a series circulation, and the left ventricle in particular must adapt immediately to dramatically increased preload from blood returning from the lungs, and increased afterload as the placental circulation is removed. The very high oxygen consumption of the newborn necessitates a high cardiac output for the first few months of life. However, animal models have demonstrated that the fetal and newborn myocardium develops less tension in response to increasing preload (sarcomere length), and that cardiac output increases less to the same degree of volume loading [9, 10]. Resting tension, however, is greater in the newborn compared to the mature heart. This information suggests that the newborn heart is operating near the top of its Frank–Starling curve, and that there is less reserve in response to both increased afterload and preload. The newborn myocardium also has only a limited ability to increase its inotropic state in response to exogenous catecholamines, and is much more dependent on heart rate to maintain cardiac output than the mature heart. One reason for this is the high levels of circulating endogenous catecholamines that appear after birth, necessary to make the transition to extrauterine life [11]. As these levels decrease in the weeks after birth, contractile reserve increases.

The neonatal myocardium is less compliant than the mature myocardium, with increased resting tension as noted previously, and a significant greater increase in ventricular pressure with volume loading [12]. This implies that diastolic function of the neonatal heart is also impaired compared to the mature heart [13]. The myofibrils of the newborn heart also appear to have a greater sensitivity to calcium, developing a greater tension than adult myofibrils when exposed to the same free calcium (Ca^{++}) concentration in vitro [14]. Table 7.2 summarizes the major physiological differences between the neonatal and mature heart [15]. With increased metabolic needs, including oxygen consumption and glucose for metabolic substrate, cardiac output indexed to weight in the neonate is double that of the adult [16] (Fig. 7.3).

Innervation of the Heart

Clinical observations in newborn infants have led to the hypothesis that the sympathetic innervation and control of the cardiovascular system is

Table 7.2 Summary of major differences between neonatal and mature hearts

	Neonatal	Mature
Physiology		
Contractility	Limited	Normal
Heart rate dependence	High	Low
Contractile reserve	Low	High
Afterload tolerance	Low	Higher
Preload tolerance	Limited	Better
Ventricular interdependence	Significant	Less
Ca^{++} cycling		
Predominant site of Ca^{++} flux	Sarcolemma	Sarcoplasmic reticulum
Dependence on normal iCa^{++}	High	Lower
Circulating catecholamines	High	Lower
Adrenergic receptors	Downregulated, insensitive β2, a1 predominant	Normal ß1 predominant
Innervation	Parasympathetic predominates; sympathetic incomplete	Complete
Cytoskeleton		
	High collagen and water content	Lower collagen/H_2O
Cellular elements		
	Incomplete SR, disorganized myofibrils	Mature SR, organized myofibrils

SR sarcoplasmic reticulum
Source: Reproduced with permission from Andropoulos and Ogletree [15]

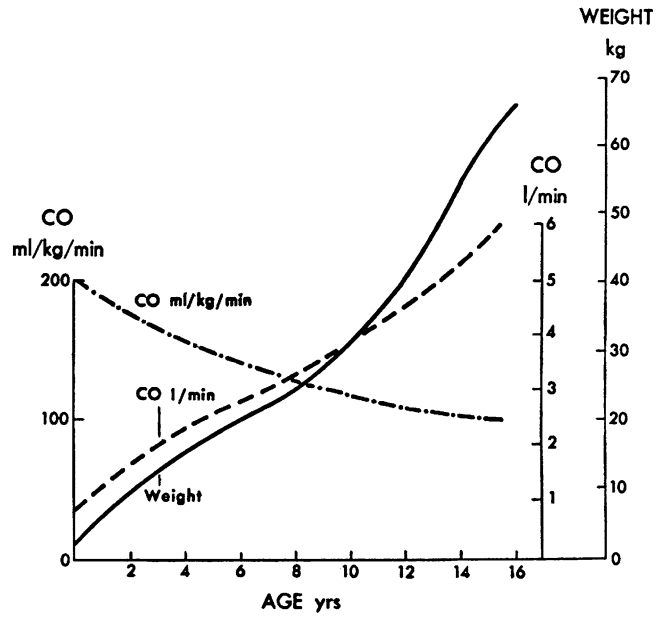

Fig. 7.3 The relationship between body weight, age, and cardiac output. Note that cardiac output in mL/min, when indexed to body weight, decreases by 50% from birth to adolescence. (Reproduced with permission from Rudolph [16])

incomplete in the newborn infant compared to older children and adults, and that the parasympathetic innervation is intact [17]. Examples of this include the frequency of bradycardia in the newborn in response to a number of stimuli, including vagal, and vagotonic agents, and the relative lack of sensitivity in the newborn to sympathomimetic agents. Histologic studies in animal models have demonstrated incomplete sympathetic innervation in the neonatal heart when compared to the adult, but no differences in the number or density of parasympathetic nerves [18, 19].

Autonomic cardiovascular control of cardiac activity can be evaluated by measuring heart rate variability in response to both respiration, and to beat-to-beat variability in systolic blood pressure [20]. The sympathetic and parasympathetic input into sinoatrial node activity contribute to heart rate variability changes with greater heart rate variability resulting from greater parasympathetic input into sinoatrial node activity [21]. Studies using these methodologies for normal infants during sleep suggest that the parasympathetic predominance gradually diminishes until approximately 6 months of age, coinciding with greater sympathetic innervation of the heart similar to adult levels [22].

Development from Child to Adult

Beyond the transition period from fetal to newborn life and into the first few months of postnatal life, there is not much human or animal information concerning the exact nature and extent of cardiac development at the cellular level. Most studies compare newborn or fetal to adult animals [23]. Cardiac chamber development is assumed to be influenced by blood flow [24]. Increases in myocardial mass with normal growth, as well as in ventricular outflow obstruction, are mainly due to hypertrophy of myocytes. Late gestational increases in blood cortisol are responsible for this growth pattern, and there is concern that antenatal glucocorticoids to induce lung maturity may inhibit cardiac myocyte proliferation. In the human infant, it is assumed that the cellular elements of the cardiac myocyte, i.e., adrenergic receptors, intracellular receptors and signaling, calcium cycling and regulation, and interaction of the contractile proteins, is similar to the adult by approximately 6 months of age. Similarly, cardiac depression by volatile agents is greater in the newborn changing to adult levels by approximately 6 months of age [25].

Normal Heart Rate and Blood Pressure Ranges at Different Ages

Heart rate must be monitored continuously by 3 or 5 lead ECG during all phases of a sedation procedure, because of the frequent effects of sedative and analgesic drugs on heart rate, and the added importance of maintaining acceptable heart rates to maintain cardiac output, especially in young infants. An understanding of the patient's baseline heart rates is important, and generally a decrease or increase of 20% or less is well tolerated and will maintain adequate cardiac output [26]. Maintaining normal sinus rhythm is obviously important, and any non-sinus rhythm needs to be diagnosed, its effect on blood pressure and cardiac output assessed, and treated if necessary. The most common arrhythmias are sinus bradycardia caused by decreased central nervous system sympathetic outflow from many sedatives, or sinus tachycardia caused by sympathomimetic effects of drugs. Slow junctional rhythms or supraventricular tachycardias are also seen during sedation procedures. It is important to understand the patient's baseline cardiac status, and rhythm, as many patients with preexisting arrhythmias will continue to experience them with sedation and no ill effects.

Blood pressure must be measured at least every 5 min during sedation procedures, and often more frequently, i.e., every 1–3 min, during the induction phase, or after a bolus of medication to deepen the level of sedation. Blood pressure is not equivalent to cardiac output, but perfusion to vital organs, especially myocardium and brain, needs to be preserved during sedation procedures and thus blood pressure should be maintained within acceptable limits, usually ±20% of the baseline blood pressure, again taking into account the patient's baseline state, and pathophysiology of any disease states. Blood pressure is usually measured with an automated oscillometric blood pressure device, and the cuff must be the proper size for the patient, according to the manufacturer's instructions. A cuff that is too small for the patient will read out a blood pressure that is falsely elevated, and a cuff that is too large will display a pressure that is spuriously low. Under normal circumstances, a cuff on the right or left upper arm is standard, although a properly-sized blood pressure cuff on the lower leg will also provide accurate measurements. The measured systolic pressure and mean pressure are very accurate

with the oscillometric devices, with the diastolic pressure being subject to increased measurement errors. Since the systolic blood pressure is most commonly used to determine high or low measurements, Table 7.3 includes this parameter for normal values. Systolic blood pressures more than 20% below baseline values, if accompanied by acceptable heart rate, oxygen saturation, and end-tidal CO_2, should be investigated and treatment such as fluid administration to increase cardiac preload and stroke volume, or decreasing the depth of sedation, should be instituted. If heart rate, SpO_2, or end-tidal CO_2 have also changed, very urgent diagnosis and treatment must be instituted, as this heralds a low cardiac output state, and possible impending cardiac arrest. Discontinuing sedation, administering fluid boluses and a vagolytic agent such as atropine or sympathomimetic agent such as ephedrine or epinephrine may be indicated. Elevated blood pressures may of course be due to inadequate sedation or analgesia, but often can be due to the drugs themselves, especially ketamine. In the latter case, the dose of ketamine should be reduced, or if sedation and analgesia judged to be inadequate, additional drugs other than ketamine should be used. Table 7.3 displays normal heart rate and systolic blood pressure for different ages.

Central Nervous System Physiology

Brain growth and development are very rapid during infancy, with the brain weight at birth about 20% of adult weight, but by 2 years of age the brain has attained 75% of adult weight [27]. The brain in the infant and young child receives a correspondingly higher percentage of the cardiac output than in the older child and adult. In addition, rapid proliferation and migration of neurons to their cortical and subcortical zones is taking place in early infancy, as is myelination and synaptogenesis [28] (Fig. 7.4). The neurotransmitters gamma-aminobutryic acid, and glutamate, and their corresponding receptors, play a crucial role in synaptogenesis, and also in the natural death of some neurons during the rapid proliferation phase (apoptosis). Most sedative agents, including benzodiazepines, barbiturates, chloral hydrate, propofol (GABA), and ketamine (NMDA) interact with these receptors giving rise to the concerns that sedative agents may increase apoptosis and potentially have adverse long-term neurodevelopmental effects [29]. Because of the relatively larger brain size and blood volume/flow, the dose per kilogram requirement for sedative agents is usually higher in the young infant to produce the desired effects than it is in the older child and adult. The exception to this is the neonate, where

Table 7.3 Normal heart rates and systolic blood pressure as a function of age

Age	Range of normal heart rates (beats per minute)	Range of normal systolic blood pressures, measured by oscillometric blood pressure device (mmHg)
Neonate (<30 days)	120–160	60–75
1–6 months	110–140	65–85
6–12 months	100–140	70–90
1–2 years	90–130	75–95
3–5 years	80–120	80–100
6–8 years	75–115	85–105
9–12 years	70–110	90–115
13–16 years	60–110	95–120
>16 years	60–100	100–125

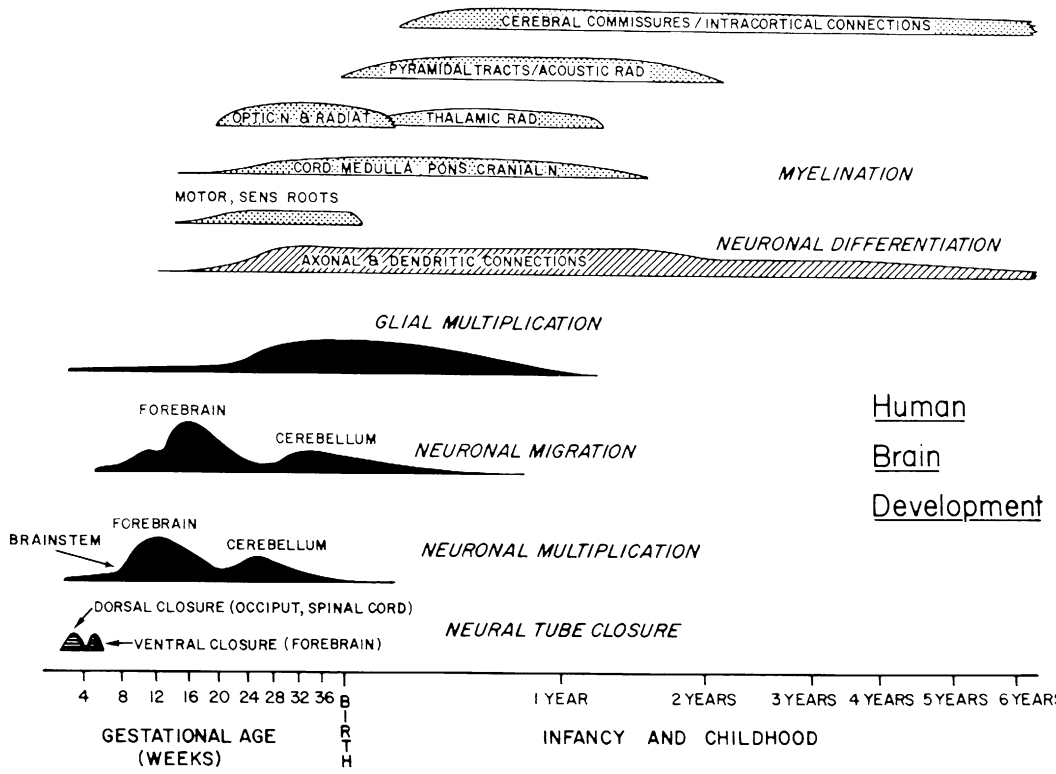

Fig. 7.4 Brain growth and development from conception to age 6 years. Note the very rapid brain growth and complexity of development from birth to age two years, when the majority of postnatal brain development occurs. This period of rapid development gives rise to the recent concerns that sedative agents interacting with gamma-aminobutryic acid and *n*-methyl-d-aspartate receptors could have long-term effects on the developing brain. See text for details. (Reproduced with permission from Kandt et al. [27])

the tight junctions of the basement membranes of the intracerebral capillaries are not fully formed, meaning the blood–brain barrier is not as fully intact, allowing passage of higher drug concentrations into neurons, causing an exaggerated effect of most drugs in this very young age group.

Cerebral autoregulation is normally intact in the full term neonate and older patient, albeit at lower blood pressures than in the adult patient. Responsiveness of the cerebral circulation to carbon dioxide tension is also intact, with significant hypercarbia causing maximal cerebral vasodilation.

Maturation of the EEG during infancy and childhood has important implications for any technology proposing to measure depth of sedation using EEG parameters. All current depth of sedation monitors using processed EEG parameters are based on the adult EEG and application of these monitors in infants and young children especially is unreliable. Infants and younger children have markedly different EEG profiles for both frequency and amplitude of EEG waveforms emanating from different regions of the brain. Older children, i.e., 8–10 years of age or older, have EEG characteristics much more similar to the adult and thus these monitors can be more reliable [30].

Developmental changes in motor, language, and behavior milestones are crucial to understand

Table 7.4 Age-specific anxieties of pediatric patients

Age	Specific type of perioperative anxiety
0–6 months	Maximum stress for parent Minimum stress for infants – not old enough to be frightened of strangers
6 months–4 years	Maximum fear of separation Not able to understand processes and explanations Significant postoperative emotional upset and behavior regression Begins to have magical thinking Cognitive development and increased temper tantrums
4–8 years	Begins to understand processes and explanations Fear of separation remains Concerned about body integrity
8 years-adolescence	Tolerates separation well Understands processes and explanations May interpret everything literally May fear waking up during surgery or not waking up at all
Adolescence	Independent Issues regarding self-esteem and body image Developing sexual characteristics and fear loss of dignity Fear of unknown

Source: Reproduced with permission from Ghazal et al. [31]

when sedating pediatric patients. Table 7.4 presents some of the important milestones in these areas [31]. In approaching the infant patient, with normal children of age 6–12 months, they will not experience stranger anxiety and thus will go with practitioners for sedation procedures with little to no protest. Extensive study and clinical experience demonstrate that infants from the premature neonate onward experience pain in the same manner as older children, and so will react accordingly to painful procedures such as IV catheter insertion. In the infant up to age 6 months, 24% sucrose, 0.2 mL placed on a pacifier and given 5–10 min before a painful procedure, will alleviate pain from venipuncture and heelsticks [32]. The mechanism of action is proposed to be endorphin release. Infants from age 6–12 months, toddlers, and preschool children up to age 5 can be expected to be quite fearful and resistant when separated from parents or familiar caregivers, and the process of separation must be planned to ameliorate this psychological discomfort as much as possible with distraction, familiar toys or objects, or having the parent present during initiation of sedation, if appropriate. School aged children of 5 of 6 years or older generally can accept simple explanations of medical procedures and will often separate from parents more easily. The patient aged 8–12 years is often the easiest to approach for sedation procedures and often has a very concrete understanding of explanations and instructions. The adolescent often has great concern about body image, and respecting this is very important. The child of any age who has been hospitalized frequently or has had prior painful or stressful experiences may be very upset at the prospect of separation from parents and sedation procedures.

Hematologic System Development

The neonate has a normal hemoglobin of 15–20 g/dL, and hematocrit of 45–60%, most all consisting of hemoglobin F, as noted earlier. Over the first 6 months of life, predominate hemoglobin species changes to adult hemoglobin A, and there is a decline to a physiologic nadir of about 11–12 g/dL of hemoglobin by 2–6 months of age. These values are maintained until about age 2 years, at which time they gradually increase in boys and girls to 12–14 g/dL by about age 12. With the onset of menstruation, hemoglobin remains at this level in girls until adulthood. In boys, hemoglobin levels continue to increase gradually to adult levels of 15–18 g/dL by age 18 [33].

The concept of a physiologic nadir of hemoglobin at 2–6 months of age is important, because this is an age when oxygen consumption is still twice that of the adult, yet oxygen carrying capacity is low, with the result that there is even less oxygen reserve in these young infants.

The blood volume of the neonate is approximately 90 mL/kg body weight, and this decreases to about 85 mL/kg by 6 months, 80 mL/kg at 1 year, and 75 mL/kg until age 2 years, after which the blood volume assumes the adult value of approximately 70 mL/kg.

Renal Physiology, and Fluid and Electrolytes

At birth the neonate has an expansion of total body water and the extracellular water space, combined with renal function that is decreased, with glomerular filtration rate only 15–30% of adult values. Renal function matures fairly rapidly, achieving levels of 50% of the adult by 2 weeks of life, and then gradually increasing to adult levels by 12 months of age [3]. Total body water also decreases to adult levels by about 12 months of age. However, fluid requirements remain high throughout the first 3–4 years of life, because of the increased body surface to weight ratio present in young children, which results in increased insensible fluid loss. Table 7.5 displays the approximate daily and hourly maintenance fluid and requirements for normal children at various weights and ages [3]. In children with normal renal function, intravenous fluids of one-quarter normal saline (38 meq NaCl/L) and 20 meq/L KCL will provide maintenance of sodium and potassium, and 5% dextrose for maintenance of glucose requirements. In actual practice, healthy infants and children over age 6 months will do well with a standard intravenous solution such as Lactated Ringer's solution during sedation procedures. This solution, which does not contain dextrose but has a sodium concentration of 130 meq/L and osmolarity similar to plasma, will allow a fluid bolus to be administered without producing hyperglycemia.

In general, modern nil per os (NPO) guidelines allowing clear liquid intake until 2 h before a sedation procedure will prevent significant fluid deficits, but frequently there are situations where the patient has been NPO for long periods of time. If NPO for greater than 6 h, many practitioners would calculate the fluid deficit accumulated during those 6 h, administer half the deficit during the first hour of the procedure, and one-quarter of the deficit in each of the next 3 h [31]. These fasting guidelines were published in 1999, approved by the American Society of Anesthesiologists (ASA) and represent a recommendation based on the review of clinical studies between 1966 and 1996, over 1,100 citations. They were intended for healthy patients undergoing elective surgery [34] (Table 7.6). The guidelines were not intended nor considered for sedation purposes, although they have been so adopted by many. A revised 2010 version of the Practice Guidelines for Preoperative Fasting is expected soon [35].

Glucose requirement is predictably high in the neonate and young infant, being 5–7 mg/kg/min in the neonate, which is 2–3 times that of the adult. The neonate and young infant less than 3–6 months of age is also prone to hypoglycemia

Table 7.5 Maintenance intravenous fluid requirements

Weight	Maintenance fluid, mL/kg/24 h	Maintenance fluid, mL/kg/h
<10 kg	100	4.16
10–20 kg	50	2.08
Each 10 kg increment above 20 kg	20	0.83

Table 7.6 American Society of Anesthesiologists' summary of fasting recommendations to reduce the risk of pulmonary aspiration[a]

Ingested material	Minimum fasting period[b] (hours)
Clear liquids[c]	2
Breast milk	4
Infant formula	6
Nonhuman milk[d]	6
Light meal[e]	6

Source: Reprinted with permission from American Association of Anesthesiologists Task Force on Preoperative Fasting [34]

[a]These recommendations apply to healthy patients who are undergoing elective procedures. They are not intended for women in labor. Following the Guidelines does not guarantee complete gastric emptying

[b]Fasting times apply to all ages

[c]Examples: water, fruit juice without pulp, carbonated beverages, clear tea, and black coffee

[d]Since nonhuman milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period

[e]A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period

because of a paucity of glycogen stores, compared to the older child and adult, thus it is especially important in this age group to encourage ingestion of clear glucose containing fluids until 2 h before a sedation procedure. And, young infants should have infusion of dextrose containing intravenous fluids during and after the sedation procedure, until they are recovered and can ingest dextrose containing fluids again.

Hepatic/Gastrointestinal Physiology

Liver function, both synthetic and metabolic, is immature at birth, with only about 30% of the functional capacity of the adult [3]. Hepatic function also matures relatively rapidly, with normal function achieved by about 3 months of life. This means that drugs which depend on hepatic metabolism for clearance, especially the cytochrome P450 system, will often have prolonged effects in the very young infant once therapeutic plasma levels are reached. In addition, coagulation factor levels are low in the neonate because of this hepatic immaturity, so that normal partial thromboplastin time, which measures coagulation function in the extrinsic coagulation system and depends on proteins synthesized in the liver, is elevated at birth to as high as 60 s. Despite this, the protein factors that inhibit coagulation are also reduced in concentration, and neonates and young infants are not more prone to clinical bleeding than older patients.

As with other systems, the brush border of the neonatal small bowel is not mature, and is more prone to insults such as infections and ischemia, particularly in the premature infant, which predisposes them to necrotizing enterocolitis. The risk of this disease diminishes greatly toward term, but the ability of the full term neonate's intestine to absorb high osmolar loads is limited. With normal intake such as breast milk or infant formulas, however, gastric emptying is rapid. This normal gastric emptying has given rise to the standard recommendation in most institutions that in patients of all ages, who do not have bowel obstruction or other condition known to delay gastric emptying, ingestion of solid food, milk, or formula until 6 h prior to a sedation procedure is acceptable. Breast milk ingestion until 4 h before sedation, and clear liquids until 2 h before, have also been shown to result in complete gastric emptying.

Temperature Regulation

Maintenance of temperature homeostasis during sedation procedures is an important goal, and the young child in particular is prone to hypothermia during prolonged sedation. Heat loss (or gain) into or from the environment is via four basic routes [36, 37]: (1) radiation: from difference in temperature between the patient and the surrounding environment, e.g., a cold room; (2) conduction: heat transfer between two surfaces in direct contact, i.e., a cold irrigating solution; (3) convection: transfer of heat to moving molecules such as air or liquid, i.e., a cold drafty MRI scanning room; (4) evaporation: loss of heat from vaporization of water from the skin or mucosal surface.

Under normal circumstances, the older infant, child, or adult will sense temperature of the blood in the anterior hypothalamus, the thermostat for the body, and use various mechanisms to keep body temperature within 0.5 of 37°C [36]. In response to mild hypothermia, the CNS via α-adrenergic sympathetic activation will cause cutaneous blood vessels to constrict, especially in the extremities, reducing blood flow and thus conserving heat by shunting warmed blood flow to deeper structures not vulnerable to radiation heat loss. With moderate hypothermia shivering occurs, which through muscle aerobic metabolism will generate additional heat and help return body temperature toward normal. With hyperthermia, initially blood flow to the extremities will remain at normal levels, but with further warming vasodilation will occur, and heat loss from radiation, convection, and conduction all increase. The next response is sweating, with the evaporation of sweat resulting in significant heat loss.

Commonly used sedative agents, including propofol and dexmedetomidine, affect the thermoregulatory thresholds [36]. In general, the higher the dose of these agents, the wider the

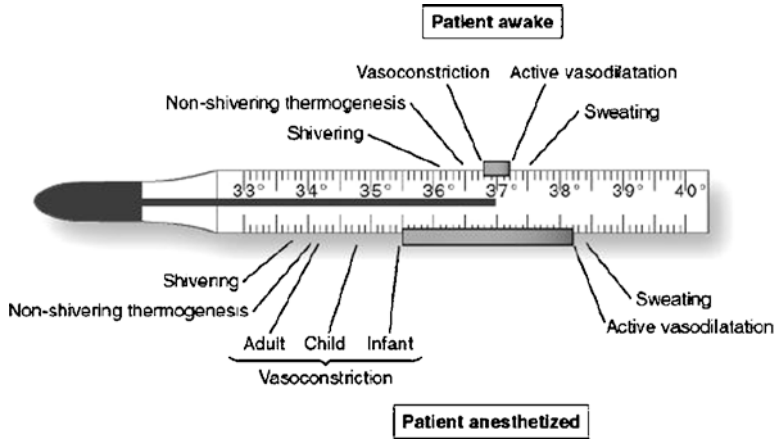

Fig. 7.5 Illustration of the thermoregulatory thresholds and gains for awake and anesthetized (sedated) infants, children, and adults in relation to the central (core) temperature. The distance between the edge of the thermometer and each effector response represents the maximal intensity of each response. The slopes of the lines (positive values for awake and negative values for anesthetized) between the thermometer and the response represent the gains of the responses. The threshold is defined as the corresponding core temperature that triggers a response. The sensitivity of the thermoregulatory system describes the range between the first cold response (vasoconstriction) and the first warm response (sweating), which is known as the interthreshold range. Sedation with agents such as propofol and dexmedetomidine produces the same dose-dependent changes in thermoregulation as general anesthesia. (Reproduced with permission from Luginbuehl and Bissonnette [37])

range of "normal" temperatures tolerated by the hypothalamus before the compensatory mechanisms described earlier occurs, meaning that temperatures will need to decrease by 1.5–2.5°C before vasoconstriction and shivering will begin, rather than 0.5°C in the awake patient (Fig. 7.5).

Adverse effects of significant hypothermia include enhanced effects of intravenous sedative medication and a lower dose requirement for sedation, as well as slowed metabolism and organ function, resulting in delayed metabolism of drugs by kidney and liver. This can result in prolonged awakening from sedation. Significant hypothermia accompanied by shivering can result in metabolic acidosis from anaerobic muscle metabolism. Significant hypothermia and shivering are also profoundly uncomfortable for the patient, often resulting in an unsatisfactory sedation experience in the case of older children, or agitation and crying behaviors in the younger children.

The neonate is a special case, as in most other organ systems, in that with significant hypothermia the neonate cannot shiver, but rather starts to metabolize special brown fat cells, mostly located between the scapulae, and in the mediastinum and perirenal areas, in order to generate heat to raise body temperature, in a process termed nonshivering thermogenesis [36]. This is accompanied by a significant catechohlamine discharge and anaerobic metabolism, resulting in lactic acidosis which can have profound secondary effects on other organ systems, i.e. the heart and circulation, resulting in hemodynamic instability. Non-shivering thermogenesis is either nonexistent or insignificant after the neonatal period.

Because of the high body surface area to weight ratio of neonates, which decreases to adult levels by 8–9 years of age, the young child is susceptible to hypothermia by radiation. Thus, an infant or young child who is uncovered and exposed to cool ambient temperatures, especially with a draft or in a room cooled because of medical equipment, e.g., MRI scanners, will cool rapidly.

Preventing hypothermia is a crucial task for every sedation procedure in children, and often the simplest method is to cover or wrap the child in warm blankets to prevent heat loss by convection. Warming the room or employing forced air

warming devices where possible, are other important measures to prevent hypothermia. Continuous temperature measurement during sedation procedures in patients at risk for hypothermia should be practiced, especially during lengthy procedures such as MRI scans in infants. Temperature should be taken along with other vital signs in the recovery area,

Drug Pharmacokinetics and Pharmacodynamics

All of the differences in organ system physiology discussed previously, especially cardiovascular, central nervous system, hepatic, renal, and body fluid composition, mean that response to sedative drugs, and initial dosage and interval dosing, are often very different especially in the infant, compared to the older child and adult.

Conclusion

Children, particularly the neonate and infant, have very substantial differences in physiology in all systems compared to the adult. The increased metabolic requirements for the rapidly growing young patient result in higher demand for oxygen and glucose, the major metabolic fuels. This increase in oxygen need limits the margin of error during sedation procedures, especially in patients less than 1 year of age, but to some extent in all growing children. The sedation practitioner must be well aware of these physiologic differences to ensure a safe and effective sedation procedure.

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Pharmacology and Clinical Application of Sedatives, Analgesics, and Adjuncts

8

Randy P. Prescilla

The overall objective in sedation outside the operating room is to provide effective and safe sedation.

The American Academy of Pediatrics (AAP) provides five specific goals: "(1) to guard the patient's safety and welfare, (2) to minimize physical discomfort and pain, (3) to control anxiety, minimize psychological trauma, and maximize the potential for amnesia, (4) control behavior and/or movement to allow the safe completion of the procedure, and (5) return the patient to a state in which safe discharge is possible" [1].

In order to achieve effective and safe sedation, it is imperative that sedation providers possess a clear understanding of the pharmacology of the drugs that will be administered. Knowledge of each drug's time of onset, peak response, and duration of action is critical [1]. The American Society of Anesthesiologists (ASA) also mandates that the curriculum for a formal training program in sedation for nonanesthesiologists should include, among others, "the pharmacology of all anesthetic drugs … of moderate sedation" [2].

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Drug Selection and Administration

The AAP states that the goals of sedation can best be achieved by selecting the lowest dose required, and selecting the drug(s) with the highest therapeutic index for the procedure. It is essential that in the selection process of which drug to use, the practitioner should choose the least number of drugs, while matching the drug(s) to the type and goal of the procedure that is being planned. For example, analgesic medications such as opioids are indicated for painful procedures, while for nonpainful procedures, sedatives/hypnotics may suffice. Since children younger than 6 years and those with developmental delay generally require deep levels of sedation, the need for deep sedation should be anticipated [1]. Anxiolysis or mild sedation may be occasionally sufficient for computerized tomography, but is often not enough in procedures such as magnetic resonance or nuclear medicine imaging.

Selection of medications and dosages should be guided by the desired key effect(s). An ideal regimen would provide acceptable analgesia, sedation, and amnesia for residual awareness of procedure-related pain or anxiety. It would cause minimal adverse effects and work reliably with a wide therapeutic index, i.e., small differences in doses would not cause over-sedation or adverse events, have rapid onset and recovery, and be easy

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to titrate to effect. No single agent or combination of agents fully achieves these goals. Selection of procedural sedation medications therefore is based upon balancing desired effects with the potential for adverse effects. For procedures that are very painful, e.g., fracture reduction, control of the pain will be paramount. For procedures that require the child to be motionless, e.g., computerized tomography (CT) or magnetic resonance imaging (MRI) scans, immobility may be most important. Most procedures in children require some combination of analgesia and immobility along with anxiolysis; therefore, sedation planning should consider all these parameters.

Because increasing depth of sedation is associated with increasing frequency of adverse events [3, 4], use of the lightest effective sedation is usually preferred. However, frequently the depth of sedation required for a particular procedure cannot be accurately predicted in a specific patient [3]. Under appreciated anxiety and a lack of comprehension in younger children and those with developmental delay, often elicit a need for deeper than anticipated sedation. For intensely painful procedures, deep sedation is typically required. Clinicians providing sedation, therefore, ideally should be trained and prepared to administer increasingly deeper sedation as guided by the patient's response to the procedure.

Careful intravenous "titration" of medications uses repeatedly administered small doses to achieve the desired clinical effect. Titration enables the practitioner to use the smallest effective dose and reduce the risk of over-sedation with its accompanying risks of respiratory depression and aspiration [3, 5–7]. Individual variation in sensitivity to the medication can also be detected, thus a smaller than expected dose may be found adequate for a given individual.

Knowledge of the time to peak effect of the specific medication is necessary to avoid "stacking" of doses when first gaining experience with titration. "Stacking" can occur after a subsequent dose is administered before the peak effect of the preceding dose has occurred. In these situations, deeper than intended sedation can easily occur. For example, morphine has a peak effect of approximately 10 min. If an additional dose of morphine is administered after 5 min because the patient is still in significant pain, by 15 min after the original dose, when both the first and second doses are near peak effects, the patient may have significant respiratory depression due to an excessive accumulative dose. For this reason, titration is difficult with drugs that have longer than 1–3 min to peak effect time.

When a "typical" total dose for a specific procedure is known, that total dose may be divided and the increments administered at intervals shorter than "the time to peak effect" without likely overshoot. This strategy of repeated administration of fractional doses for fixed dose protocols, e.g., half of the anticipated total dose administered twice with administration separated by a short interval, reduces the risk for significant respiratory depression induced by some agents such as the combined technique using fentanyl and midazolam. This approach is suggested for providers as they acquire experience with a specific medication.

Use of Multiple Drugs for Sedation

A strong knowledge of pharmacology is essential when administration of several sedating agents is considered. Drugs with long durations of action must be allowed to manifest their pharmacologic actions and peak effects before additional doses are considered. The practitioner must know whether the previous dose of any drug has taken full effect before administering additional medications [1].

If the mechanisms of action of concomitant medications are similar, synergistic effects may be potentiated, and the risk of adverse events is magnified. Respiratory depression is a common pathway of adverse events, and may result unexpectedly and quickly. A study in 2000 showed that potential for adverse events may be increased when three or more medications are administered for sedation [8].

Practitioners must also be cognizant that drug interactions may occur. Drugs such as erythromycin, cimetidine, and others inhibit the cytochrome P450 system and concomitant use of these medications can result in prolonged sedation with midazolam and other medications

that compete for the same enzyme systems. Even herbal medications such as St. John's wort or echinacea can affect drug pharmacokinetics resulting from altered cytochrome P450 effects.

Additional Pharmacologic Effects

One benefit that some sedatives provide is analgesia. This is critical not only for patients who are in pain at the onset of sedation but also for patients who will become uncomfortable or experience pain during the diagnostic study. Patient as well as procedural factors can amplify the pain response: for example, a child with scoliosis who may be required to lay flat on an MRI table for an hour, or a child whose elbow will need to remain flexed at a certain angle during a radiologic imaging study. By their nature as opioids, fentanyl, sufentanil, remifentanil, and alfentanil are known to produce analgesia. Dexmedetomidine has also been reported to provide analgesic effects.

An additional effect that some sedatives provide is relative amnesia. This effect is helpful for young children whose previous visit(s) may be marred by traumatic memory. An amnestic effect is also most helpful in children who will need additional sedation or procedures in the future. Drugs that have been reported to produce amnesia include propofol [9–12], fentanyl [9], ketamine [12, 13] and S-ketamine [14], and the benzodiazepines midazolam [15, 16] and lorazepam [17]. Ideally, the patient will be unable to recall procedure-related pain despite occasional moans or cries out during intensely painful parts of the procedure [18]. It is unwise to promise complete amnesia during the informed consent process.

Off-Label Use

Unfortunately, most drugs used for sedation in children do not carry pediatric information that have been reviewed and approved by the Food and Drug Administration (FDA) and as such, these drugs are used "off-label." It is estimated that only about 20% of drugs approved by the FDA are labeled for pediatric use. The situation is even more acute in neonates and most specially, premature neonates.

Readers are reminded that the current FDA guidelines on off-label use state that "if physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects" [19].

In general, the off-label use of a marketed product for the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) from the FDA [19]. However, the institution at which the product will be used may, under its own authority, require Institutional Review Board (IRB) review or other institutional oversight. The reader is advised to consult the IRB in his or her institution for specific guidelines.

Alternate Sites of Administration

Off-label use in pediatrics includes the use of routes of administration that are not contained in current FDA-approved drug information. Pediatric practitioners try to be innovative in order to decrease pain and discomfort in children through a variety of ways. These include drug administration via nasal, transdermal, oral, sublingual, and oral and rectal routes. The American Academy of Pediatrics, Committee on Drugs cautions that although new routes of administration offer advantages, controlled laboratory and clinical trials are necessary to determine safe use. When new methods or routes of drug administration are introduced, the Committee further recommends that the practitioner understand the pharmacologic actions of the drug, as well as the pharmacokinetic and pharmacodynamic implications that may be unique for pediatric patients [20].

Reversal Agents

The knowledge of pharmacology should also extend to that of drugs that may be needed to "rescue" a sedated patient. Currently, pharmacologic

antagonists exist only for opiates and benzodiazepines. This includes reversal agents such as flumazenil (Flumazepil, Anexate, Lanexat, Mazicon, Romazicon) and naloxone (Narcan, Nalone, Narcanti). Drugs which are not reversal agents per se such as albuterol (Salbutamol, Ventolin, Aerolin, Ventorlin, Asthalin, Asthavent, Proventil, ProAir), ammonia spirits, atropine, diphenhydramine (Benadryl, Dimedrol, Daedalon), diazepam, epinephrine (Adrenaline), glucose, lidocaine (intracardiac and local infiltration), methylprednisolone (Medrol, Solu-Medrol, Cadista), fosphenytoin (Cerebyx, Prodilantin), rocuronium, sodium bicarbonate, and succinylcholine (Suxamethonium chloride, Suxamethonium, Anectine, Quelicin, Scoline) may also be required in specific cases [1]. As the need for resuscitation can occur unexpectedly, the practitioner should familiarize him or herself with dosing and drug administration.

The Effects of Psychotropic Drugs on the Developing Brain

There is growing concern about the neurotoxic effects of anesthetics in the human developing brain [21]. To date, there is no evidence in humans of neurotoxicity.

Formulary

The most common medications currently used in sedation in children are presented in the next section. A brief description of the pharmacologic nature of each drug is provided, along with any available pediatric pharmacokinetic data, followed by a brief discussion on the clinical applications in children and common adverse events.

As the data indicate, there are limited published pediatric data on most of these medications. The sedation provider is encouraged to consult the latest appropriate formulary in their institution, particularly for pediatric dosage and restrictions of use, if any. Pediatric sedation providers are also encouraged to conduct formal clinical studies to add to the literature in pediatric sedation.

This chapter is not intended to list which drugs are appropriate for which particular procedure. The reader is advised to refer to the individual chapters which discuss specific sedatives in the appropriate clinical context, for indications and dosages.

Lastly, inclusion of a drug in this chapter does not imply endorsement of an off-label use.

Sedatives and Analgesics

Alfentanil (Alfenta, Rapifen)

Drug Class: Opioid.

Route of administration: Primarily intravenous, although intranasal administration in children has been reported [22, 23].

The pharmacokinetics of alfentanil can be described as a three-compartment model. The liver is the major site of biotransformation; urinary excretion is the major route of elimination of metabolites [24].

The pharmacokinetics of alfentanil in children has been described [23, 25–35].

Contraindications: Alfentanil is contraindicated in patients with known hypersensitivity to the drug or known intolerance to other opioid agonists.

Clinical application: Alfentanil is an opioid analgesic with a rapid onset of action. As such it is used in sedation as an analgesic adjunct in anesthesia or monitored anesthesia care.

Alfentanil is seldom used now [36].

Common adverse events [24] include respiratory depression and skeletal muscle rigidity, particularly of the truncal muscles. Alfentanil may produce muscular rigidity that involves the skeletal muscles of the neck and extremities.

Respiratory events reported during Monitored Anesthesia Care included hypoxia, apnea and bradypnea, nausea, hypotension, vomiting, pruritus, confusion, somnolence, and agitation.

The incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher reported incidence in patients undergoing gynecologic surgery. The overall reports of nausea and vomiting with alfentanil were comparable to fentanyl.

Chloral hydrate

Drug Class: Chloral derivative. Chloral hydrate is rapidly reduced to the active compound trichloroethanol which exerts barbiturate-like effects on $GABA_A$-receptor [37].

Route of administration reported: Primarily oral, but rectal administration for sedation in children has been reported [38–41].

Chloral hydrate is extensively metabolized in the liver by alcohol dehydrogenases and by erythrocytes to its major metabolite, trichloroethanol [42]. Less than 10% of chloral hydrate is excreted in the urine.

The pharmacokinetics of chloral hydrate in children has been described [43, 44].

Approved indications: Sedative, hypnotic. (+) Pediatric labeling.

Contraindications: Chloral hydrate is contraindicated in patients with marked hepatic or renal impairment and in patients who have previously demonstrated hypersensitivity or an idiosyncratic reaction to the drug.

Clinical application: Chloral hydrate continues to be used for moderate sedation in children. The advantages and disadvantages of chloral hydrate have been reviewed [45]. Disadvantages include the long half-life: up to 48 h in children [43]. TCE has also been found to be carcinogenic in mice [45, 46].

In 1993, the AAP issued a statement on the use of chloral hydrate for sedation in children [46]. In it, the Academy states that it is an effective sedative when administered in the recommended dosage. However, repetitive dosing of chloral hydrate is of concern, as well as theoretical long-term risk of carcinogenicity. The need for additional studies was raised.

Common adverse events include prolonged sedation, respiratory depression, nausea/vomiting, gastric and esophageal irritation, diarrhea, headache, disorientation, dysphoria, dizziness, rash, and hypotension (especially in neonates).

Dexmedetomidine (Precedex)

Drug Class: Alpha2 receptor agonist.

Route of administration: Intravenous [47], although buccal [48–51], intranasal [52–54] administration in children has been reported.

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450-mediated metabolism. About 95% of the drug is recovered in the urine and 4% in the feces.

The pharmacokinetics of dexmedetomidine in children has been described [55–59].

Approved indications: Sedation

Contraindication: None

Clinical application: Dexmedetomidine was originally indicated for sedation of initially intubated and mechanically ventilated adult patients during treatment in an intensive care setting. It has recently been approved for sedation of nonintubated adults prior to and/or during surgical and other procedures.

Dexmedetomidine offers the advantage of providing sedation and analgesia with little respiratory depression and in most a tolerable decrease in blood pressure and heart rate [60].

Adverse events [47] include the following serious adverse reactions: hypotension, bradycardia, sinus arrest, and transient hypertension in both Intensive Care Unit and procedural sedation studies.

Hypotension and bradycardia were the most common adverse reactions associated with the use of dexmedetomidine during postapproval use.

Diazepam (Valium, Antenex)

Drug Class: Benzodiazepine.

Route of administration: Rectal, intravenous, oral

After oral administration >90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1–1.5 h with a range of 0.25–2.5 h. Absorption is delayed and decreased when administered with a moderate fat meal.

Diazepam is N-demethylated to the active metabolite *N*-desmethyldiazepam, and is hydroxylated to the active metabolite temazepam. *N*-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation. The initial distribution phase is followed by a prolonged terminal elimination phase (half-life

up to 48 h). The terminal elimination half-life of the active metabolite *N*-desmethyldiazepam is up to 100 h. Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates [61].

The clinical pharmacology of diazepam in children has been reviewed [62].

Approved indications: Sedation. (+) Pediatric labeling.

Contraindications: Diazepam injection is contraindicated in patients with a known hypersensitivity to this drug, in acute narrow angle glaucoma and in open angle glaucoma unless patients are receiving appropriate therapy.

Clinical application: Diazepam is usually administered to provide anxiolysis, with accompanying mild sedation. This state usually suffices for short diagnostic procedures.

Diazepam may be orally administered 20–30 min before the procedure.

Common adverse events include drowsiness, fatigue, and ataxia; venous thrombosis and phlebitis at the site of injection [61].

Etomidate (Amidate)

Drug Class: Carboxylated imidazole.

Route of administration: Intravenous.

Etomidate is rapidly metabolized in the liver. Approximately 75% of the administered dose is excreted in the urine during the first day after injection. The chief metabolite is produced from hydrolysis of etomidate, and accounts for about 80% of the urinary excretion [63].

The pharmacokinetics of etomidate in children has been described [64].

Contraindication: Etomidate is contraindicated in patients who have shown hypersensitivity to it.

Clinical application: Etomidate was used for computed tomography sedation in the emergency department and was more effective and efficient than pentobarbital, with rare adverse events [65]. The use of etomidate for sedation has also been compared to midazolam [66] and pentobarbital [67].

Common adverse events [63] include transient venous pain on injection and transient skeletal muscle movements, including myoclonus, hyperventilation, hypoventilation, apnea of short duration, laryngospasm, hiccup, and snoring suggestive of partial upper airway obstruction have been observed in some patients; hypertension, hypotension, tachycardia, bradycardia, and other arrhythmias have occasionally been observed during induction; and maintenance of anesthesia, nausea, and/or vomiting following induction of anesthesia. One case of severe hypotension and tachycardia, judged to be anaphylactoid in character, has been reported.

Fentanyl (Fentanil, Sublimaze, Actiq, Durogesic, Duragesic, Fentora, Onsolis, Instanyl, Abstral)

Drug Class: A synthetic opioid related to the phenylpiperidines [68].

Route of administration: Primarily intravenous, epidural, and intrathecally. Transdermal [69–75], intranasal [76–89], and transmucosal administration [90–116] in children have been reported.

Fentanyl is primarily transformed in the liver, and is excreted mainly through the kidneys, mostly as metabolites with less than 10% representing the unchanged drug.

The pharmacokinetics of fentanyl in children has been described [117–119].

Contraindication: Fentanyl is contraindicated in patients with known intolerance to the drug.

Clinical application: Fentanyl remains popular drug for sedation because of its relatively shorter time to peak effect, rapid termination of effect after small bolus doses, and relative cardiovascular stability. Its intravenous use has been effective but limited by clinical concerns about muscle rigidity [36].

Common adverse events include respiratory depression, apnea, rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression, or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis. Secondary rebound respiratory depression may occasionally occur postoperatively [68].

When a tranquilizer such as droperidol is used with fentanyl citrate, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 h postoperatively. When

they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents. Postoperative drowsiness is also frequently reported following the use of droperidol [68].

Fospropofol (Lusedra)

Drug Class: Alkylphenol derivative.

Route of administration: Intravenous.

Fospropofol is a water-soluble prodrug of propofol (see below). Since it is water soluble, fospropofol eliminates some of the known lipid emulsion-associated disadvantages of propofol such as pain on injection, narrow therapeutic window with the potential to cause deep sedation, high lipid intake during long-term sedation, and risk of infection resulting from bacterial contamination [120].

Fospropofol is metabolized in vivo to produce liberated propofol (producing the sedative effect), phosphate, and formaldehyde [121].

The use and the pharmacokinetics of fospropofol in children have not been described.

Approved indications: Monitored Anesthesia Care sedation.

Contraindications: None.

Clinical application: The pharmacokinetic and pharmacodynamic profiles of fospropofol make it an attractive agent for sedation for procedures of short duration. It is approved for use as a sedative-hypnotic for Monitored Anesthesia Care in adult patients undergoing diagnostic or therapeutic procedures.

Common adverse events include paresthesia and pruritus. The most commonly reported reasons for discontinuation are paresthesia and cough. Serious adverse reactions include respiratory depression, hypoxemia, loss of purposeful responsiveness, and hypotension [122].

Ketamine (Ketanest, Ketaset, Ketalar)

Drug Class: Phencyclidine derivative.

Route of administration: Intravenous and intramuscular.

Ketamine is rapidly absorbed following parenteral administration and rapidly distributed into body tissues. Ketamine undergoes N-dealkylation (metabolite I), hydroxylation of the cyclohexone ring (metabolites III and IV), conjugation with glucuronic acid, and dehydration of the hydroxylated metabolites to form the cyclohexene derivative (metabolite II). Water-soluble conjugates are excreted in the urine [123].

The pharmacokinetics of ketamine in children has been described [124–128].

Contraindications: Ketamine is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and in those who have shown hypersensitivity to the drug.

Clinical application: Ketamine is a rapid-acting dissociative agent that produces an anesthetic (dissociative anesthesia) state characterized by profound analgesia, normal pharyngeal–laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression.

Ketamine is used for premedication, sedation, and induction and maintenance of general anesthesia, which is then termed "dissociative anaesthesia." Ketamine and its S(+)-isomer are ideal anesthetic agents for trauma victims, patients with hypovolemic and septic shock, and patients with pulmonary diseases. Even subanesthetic doses of this drug have analgesic effects, so ketamine is also recommended for postoperative analgesia and sedation. The combination of ketamine with midazolam or propofol can be extremely useful and safe for sedation and pain relief in intensive care patients, especially during sepsis and cardiovascular instability [129].

The evolution of the applications of ketamine in children has been reviewed recently [130].

Common adverse events include the following [123]:

Cardiovascular: Hypertension and tachycardia are common, although hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of ketamine. Laryngospasms and other forms of airway obstruction have occurred.

Eye: Diplopia and nystagmus have been noted. Ketamine may also cause a slight elevation in intraocular pressure measurement.

Psychological: Emergence reactions have been reported.

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures.

Gastrointestinal: Mild to moderate anorexia, nausea, and vomiting have been observed.

General: Anaphylaxis, local pain, and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

Lorazepam (Ativan, Temesta)

Drug Class: 3-hydroxyl benzodiazepine.

Route of administration: Oral, intravenous, intramuscular.

Lorazepam is extensively conjugated to the 3-0-phenolic glucuronide in the liver and is known to undergo enterohepatic recirculation. Lorazepam glucuronide is an inactive metabolite and is eliminated mainly by the kidneys [131].

The pharmacokinetics of lorazepam in pediatrics has been described [132, 133].

Contraindications: Lorazepam injection is contraindicated in patients with a known sensitivity to benzodiazepines or its vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol), in patients with acute narrow-angle glaucoma, or in patients with sleep apnea syndrome. It is also contraindicated in patients with severe respiratory insufficiency, except in those patients requiring relief of anxiety and/or diminished recall of events while being mechanically ventilated. The use of lorazepam injection intra-arterially is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation.

Clinical application: Lorazepam has been used to provide anxiolysis as well as preanesthetic medication. Compared to midazolam, lorazepam has a less rapid onset of action and a longer duration of action.

Common adverse events [131] include depression of the central nervous system. Excessive sleepiness and drowsiness were the most common consequences of CNS depression. Other symptoms include restlessness, confusion, depression, crying, sobbing, and delirium. Visual hallucinations were present in about 1% and were self-limiting. Hypertension and hypotension have occasionally been observed.

As with all benzodiazepines, paradoxical reactions such as stimulation, mania, irritability, restlessness, agitation, aggression, psychosis, hostility, rage, or hallucinations may occur in rare instances and in an unpredictable fashion.

Fatalities also have been reported, usually in patients on concomitant medications (e.g., respiratory depressants) and/or with other medical conditions (e.g., obstructive sleep apnea).

Meperidine (Demerol, Isonipecaine, Lidol, Pethanol, Piridosal, Algil, Alodan, Centralgin, Dispadol, Dolantin, Mialgin, Petidin Dolargan, Dolestine, Dolosal, Dolsin, Mefedina)

Drug Class: Opioid.

Route of administration: Intramuscular, subcutaneous, and slow intravenous.

The onset of action is slightly more rapid than with morphine, and the duration of action is slightly shorter. Meperidine is significantly less effective by the oral than by the parenteral route, but the exact ratio of oral to parenteral effectiveness is unknown.

Meperidine is metabolized chiefly in the liver, and extensively excreted by the kidney [134].

The pharmacokinetics of meperidine in pediatrics has been described [135].

Contraindications: Meperidine is contraindicated in patients who have shown hypersensitivity to it.

Meperidine is also contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear, but may be related to a preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension and have resembled the syndrome of acute narcotic overdose. In other reactions, the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension.

Although it is not known that other narcotics are free of the risk of such reactions, virtually all of the reported reactions have occurred with meperidine.

Clinical application: Meperidine, in 60–80 mg parenteral doses, is approximately equivalent in analgesic effect to 10 mg of morphine. It has been used to provide analgesia and sedation in children over the past several decades.

Common adverse events include respiratory depression and, to a lesser degree, circulatory depression; respiratory arrest, shock, and cardiac arrest have occurred [134].

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating.

Methohexital (Methohexitone, Brevital)

Drug Class: Barbiturate.

Route of administration: Intravenous, rectal.

Unlike thiopental and thiamylal, methohexital has a much more rapid clearance and therefore accumulates less during prolonged infusions. All three are primarily eliminated by hepatic metabolism and renal excretion of inactive metabolites [136, 137].

The pharmacokinetics of methohexital in pediatrics has been described [138–145].

Contraindications: Methohexital is contraindicated in patients in whom general anesthesia is contraindicated, in those with latent or manifest porphyria, or in patients with a known hypersensitivity to barbiturates.

Clinical application: Methohexital is labeled for use in pediatric patients older than 1 month: (1) for rectal or intramuscular induction of anesthesia prior to the use of other general anesthetic agents, (2) for rectal or intramuscular induction of anesthesia and as an adjunct to subpotent inhalational anesthetic agents for short surgical procedures, and (3) as rectal or intramuscular anesthesia for short surgical, diagnostic, or therapeutic procedures associated with minimal painful stimuli.

Methohexital is threefold more potent than thiopental and thiamylal.

Common adverse events include extensions of pharmacologic effects such as:

Cardiovascular: Circulatory depression, thrombophlebitis, hypotension, tachycardia, peripheral vascular collapse, and convulsions in association with cardiorespiratory arrest.

Respiratory: Respiratory depression (including apnea), cardiorespiratory arrest, laryngospasm, bronchospasm, hiccups, and dyspnea.

Neurologic: Skeletal muscle hyperactivity (twitching), injury to nerves adjacent to injection site, and seizures.

Psychiatric: Emergence delirium, restlessness, and anxiety may occur, especially in the presence of postoperative pain.

Gastrointestinal: Nausea, emesis, abdominal pain, and liver function tests abnormal.

Allergic: Erythema, pruritus, urticaria, and cases of anaphylaxis have been reported rarely.

Other adverse reactions include pain at injection site, salivation, headache, and rhinitis.

Midazolam (Versed, Dormicum, Hypnovel)

Drug Class: Benzodiazepine.

Route of administration: Intravenous and oral.

The absolute bioavailability of the midazolam administered through the intramuscular route was greater than 90%. The peak concentrations for midazolam and its 1-hydroxy metabolite were approximately one-half of those achieved after intravenous injection.

Midazolam is approximately 97% bound to plasma protein, principally albumin.

Elimination of the parent drug takes place via hepatic metabolism mediated by cytochrome P450-3A4 to hydroxylated metabolites that are conjugated and excreted in the urine [146].

The pharmacokinetics of midazolam in pediatrics has been described [147–166].

Approved indications: Sedation, induction of anesthesia, component of balanced anesthesia. (+) Pediatric labeling

Contraindications: Midazolam is contraindicated in patients with a known hypersensitivity to the drug. Midazolam, like other benzodiazepines, is contraindicated in patients with acute narrow-angle glaucoma. Midazolam, like other benzodiazepines, may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy.

Clinical application: Midazolam is usually administered to provide anxiolysis, with accompanying mild sedation. This state usually suffices for short diagnostic procedures.

For children who do not require placement of an intravenous line, the parenteral formulation of midazolam may be orally administered 15–30 min before the procedure.

Common adverse events in pediatrics include desaturation, apnea, hypotension, paradoxical reactions, hiccough, seizure-like activity, and nystagmus. The majority of airway-related events occurred in patients receiving other CNS depressing medications and in patients where midazolam was not used as a single sedating agent.

Neonates: For information concerning hypotensive episodes and seizures following the administration of midazolam hydrochloride to neonates.

Morphine (MS Contin, MSIR, Avinza, Kadian, Oramorph, Roxanol, Kapanol)

Drug Class: Opioid.

Route of administration: Intravenous, intramuscular, rectal.

Morphine is conjugated with glucuronic acid to form two major metabolites: Morphine-6-glucuronide and morphine-3-glucuronide. The former has similar pharmacological actions compared to morphine. Both metabolites are excreted by the kidney [167].

The pharmacokinetics of morphine in pediatrics has been well described [168–187].

Contraindications: Morphine is contraindicated in those medical conditions which would preclude the administration of opioids by the intravenous route: allergy to morphine or other opiates, acute bronchial asthma, and upper airway obstruction. Morphine, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or a concurrent administration of drugs, such as phenothiazines or general anesthetics.

Clinical application: Morphine and other opioid agonists exert a wide range of physiological effects. In sedation, the most pertinent effects are analgesia, drowsiness, changes in mood, and mental clouding. At therapeutic levels, patients report that the pain is less intense, less discomforting, or entirely gone; drowsiness commonly follows [36].

Common adverse events include respiratory depression and/or respiratory arrest. This depression and/or respiratory arrest may be severe and could require intervention. Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. Single-dose neuraxial administration may result in acute or delayed respiratory depression for periods at least as long as 24 h [167].

In general, side effects are amenable to reversal by narcotic antagonists.

Nitrous oxide

Route of administration: Inhaled.

Nitrous oxide (N_2O) is a colorless, odorless, tasteless gas that produces dissociative euphoria, drowsiness, and a "floating sensation" with anxiolysis and mild to moderate amnesia and analgesia.

The pharmacokinetics of nitrous oxide in children has been described [188, 189].

Contraindications: Nitrous oxide should not be used with any condition where air is entrapped within a body and where its expansion might be dangerous: Artificial, traumatic or spontaneous pneumothorax, air embolism, decompression sickness, following a recent dive, following air encephalography, severe bullous emphysema, use during myringoplasty, and gross abdominal distension.

Clinical application: Nitrous oxide is used primarily for anxiolysis, mild analgesia, and amnesia during brief procedures, especially in conjunction with local anesthesia, e.g., laceration repair, abscess incision and drainage, lumbar puncture, intravenous line placement, and some fracture reductions. Its advantages include rapid onset of action (within 5 min), and N_2O does not require vascular access or painful administration. Recovery from N_2O sedation typically is very rapid, with the child able to sit alone within 5 min and ready for discharge within 15 min [190].

The use of nitrous oxide in children for sedation has been reported [190–209].

Common adverse events include vomiting, nausea, inadequate sedation, agitation/delirium, apnea >15 s, oxygen saturation 89%, unresponsive

episode with oxygen saturation 83%, stridor, seizure, diaphoresis, burpy/hiccupy, gaggy, expectorated large amount of clear phlegm, and screaming [210].

Pentobarbital (Nembutal)

Drug Class: Barbiturate.

Route of administration: Primarily intravenous, although oral administration has been reported in children [211].

Barbiturates are absorbed and rapidly distributed to all tissues and fluids with high concentrations in the brain, liver, and kidneys. Pentobarbital is metabolized primarily by the hepatic microsomal enzyme system, and the metabolic products are excreted in the urine, and less commonly, in the feces [212].

The pharmacokinetics of pentobarbital in children has been described [213, 214].

Approved indications: Sedative-hypnotic, induction of anesthesia. (+) Pediatric labeling.

Contraindications: Pentobarbital is contraindicated in patients with known barbiturate sensitivity. It is also contraindicated in patients with a history of manifest or latent porphyria.

Clinical application: Pentobarbital is a widely used barbiturate used for sedation of children. However, its delayed onset of action and prolonged sedation has led to the use of other medications for sedation. The occurrence of paradoxic hyperactivity reactions has also contributed to the decline in its use.

Common adverse event include somnolence (most common). Other adverse events include agitation, confusion, hyperkinesia, ataxia, CNS depression, nightmares, nervousness, psychiatric disturbance, hallucinations, insomnia, anxiety, dizziness, and thinking abnormality. Respiratory effects include hypoventilation and apnea. Cardiovascular system: Bradycardia, hypotension, and syncope. Digestive system: Nausea, vomiting, and constipation. Other reported reactions: Headache, injection site reactions, hypersensitivity reactions (angioedema, skin rashes, exfoliative dermatitis), fever, liver damage, and megaloblastic anemia following chronic phenobarbital use [212].

Propofol (Diprivan)

Drug Class: Alkylphenol derivative.

Route of administration: Intravenous.

Propofol is extensively distributed and rapidly cleared from the body. Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in the urine [215].

The pharmacokinetics of propofol in children has been described [216–234].

Approved indications: Initiation of Monitored Anesthesia Care sedation, combined sedation and regional anesthesia, induction and maintenance of general anesthesia, and Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients. (+) Pediatric labeling (induction and maintenance of general anesthesia).

Contraindications: Propofol injectable emulsion is contraindicated in patients with a known hypersensitivity to propofol injectable emulsion or any of its components. It is contraindicated in patients with allergies to eggs, egg products, soybeans, or soy products.

Clinical application: Propofol is a rapidly acting anesthetic used in the induction and maintenance of general anesthesia, as well as in sedation. Propofol sedation is of a similar quality to that produced by midazolam. Emergence from sedation occurs quickly due to its rapid clearance.

The use of propofol in children for sedation has been recently compared to midazolam [235], midazolam and fentanyl [236], pentobarbital [237], midazolam + pentobarbital + fentanyl [238], ketamine [239], midazolam + ketamine [240], and dexmedetomidine [241, 242].

The adverse events in 49,836 pediatric sedations with propofol in 37 centers were recently reviewed [243].

The use of propofol by nonanesthesiologists was discussed in several chapters.

Common adverse events include apnea in pediatric patients. Adverse events in adults include bradycardia, arrhythmia, tachycardia nodal, hypotension, decreased cardiac output, hypertension, hypotension, burning/stinging or pain at the site of injection, hyperlipidemia, apnea, respiratory acidosis, rash, and pruritus.

Remifentanil (Ultiva)

Drug Class: A 4-anilidopiperidine derivative of fentanyl.

Route of administration: Intravenous.

Unlike other opioids, remifentanil is rapidly metabolized by hydrolysis of the propanoic acid-methyl ester linkage by nonspecific blood and tissue esterases. This metabolite has minimal activity. The pharmacokinetics of remifentanil is unaffected by the presence of renal or hepatic impairment [244].

The pharmacokinetics of remifentanil in children has been described [245, 246].

Contraindications: Due to the presence of glycine in the formulation, remifentanil is contraindicated for epidural or intrathecal administration. Remifentanil is also contraindicated in patients with known hypersensitivity to fentanyl analogs.

Clinical application: Remifentanil has been shown to be effective in providing analgesia-based sedation in pediatric ICU patients requiring mechanical ventilation, in newborns requiring mechanical ventilation, and in another group of children who were being mechanically ventilated postoperatively [247].

The use of remifentanil in children (in Europe) has recently been reviewed [248, 249].

Common adverse events include nausea, vomiting, and shivering in children. Other adverse events reported in children include onset of rhonchi, postoperative complication, stridor, and cough.

S-ketamine (Ketanest, Ketaset, Ketalar)

Drug Class: Phencyclidine derivative; S-ketamine is the active isomer of ketamine [250].

Route of administration: Primarily intravenous, although intranasal [251], caudal block [252–258] and rectal [259–261] administration in children have been reported.

Ketamine is rapidly absorbed following parenteral administration and rapidly distributed into body tissues. Ketamine undergoes N-dealkylation (metabolite I), hydroxylation of the cyclohexene ring (metabolites III and IV), conjugation with glucuronic acid and dehydration of the hydroxylated metabolites to form the cyclohexene derivative (metabolite II). Water-soluble conjugates are excreted in the urine [250].

The pharmacodynamics [262] and the pharmacokinetics [263, 264] of S-ketamine in children have been described.

Contraindications: S-ketamine is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and in those who have shown hypersensitivity to the drug.

Clinical application: Clinically, the anesthetic potency of the S(+)-isomer is approximately three to four times that of the R(−)-isomer.

Ketamine is a rapid-acting general anesthetic producing an anesthetic (dissociative anesthesia) state characterized by profound analgesia, normal pharyngeal–laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression.

Like ketamine, S(+)-ketamine is used for premedication, sedation, and induction and maintenance of general anesthesia, which is then termed "dissociative anaesthesia." Ketamine and its S(+)-isomer are ideal anesthetic agents for trauma victims, patients with hypovolemic and septic shock, and patients with pulmonary diseases. Even subanesthetic doses of this drug have analgesic effects, so ketamine is also recommended for postoperative analgesia and sedation. The combination of ketamine with midazolam or propofol can be extremely useful and safe for sedation and pain relief in intensive care patients, especially during sepsis and cardiovascular instability.

Common adverse events are similar to those reported for ketamine.

Sufentanil (Sufenta)

Drug Class: Opioid.

Route of administration: Intravenous.

Sufentanil has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. Within anesthetic dosages, recovery times are more rapid compared to equipotent fentanyl dosages. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 h and

only 2% of the dose is eliminated as unchanged drug [265].

The elimination half-life of sufentanil is shorter in infants and children, and longer in neonates compared to that of adolescents and adults. The pharmacokinetics of sufentanil in children has been described [266–269].

Contraindications: Sufentanil is contraindicated in patients with known hypersensitivity to the drug or known intolerance to other opioid agonists.

Clinical application: Sufentanil has been reported to be as much as 5–10 times as potent as fentanyl.

At intravenous doses of up to 8 μg/kg, sufentanil is an analgesic component of general anesthesia; at intravenous doses ≥8 μg/kg, sufentanil produces a deep level of anesthesia. Sufentanil produces a dose-related attenuation of catecholamine release, particularly norepinephrine.

At intravenous dosages of ≥8 μg/kg, sufentanil produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages.

Common adverse events include respiratory depression and skeletal muscle rigidity, particularly of the truncal muscles. The return of normal bladder activity may be delayed. Hypotension was observed 7 times more frequently in intravenous trials than in epidural trials.

Reversing Agents

Flumazenil (Flumazepil, Anexate, Lanexat, Mazicon, Romazicon, Anexate)

Drug Class: Imidazobenzodiazepine.

Route of administration: Primarily intravenous [270], although intramuscular [271], intranasal [272, 273], oral [271], and rectal [274–277] administration in children have been reported.

Flumazenil is completely metabolized in the liver. Elimination is essentially complete within 72 h, with 90–95% appearing in urine and 5–10% in feces.

The pharmacokinetics of flumazenil in children has been described [277, 278].

Contraindications: Flumazenil is contraindicated in patients with a known hypersensitivity to flumazenil or benzodiazepines, patients who have been given a benzodiazepine for control of a potentially life-threatening condition (e.g., control of intracranial pressure or status epilepticus), and in patients who are showing signs of serious cyclic antidepressant overdose.

Clinical application: Flumazenil is a benzodiazepine receptor antagonist. Its primary use in sedation is to reverse sedation resulting from the administration of benzodiazepines such as diazepam, lorazepam, midazolam, and temazepam.

Common adverse events include convulsions in patients with severe hepatic impairment and in patients who were relying on benzodiazepine effects to control seizures, who were physically dependent on benzodiazepines, or who had ingested large doses of other drugs (mixed-drug overdose). Serious adverse reactions include deaths, the majority of which occurred in patients with serious underlying disease or in patients who had ingested large amounts of nonbenzodiazepine drugs (usually cyclic antidepressants), as part of an overdose. Six of the 446 adult patients who received flumazenil in controlled clinical trials for the management of a benzodiazepine overdose had seizures [270].

Naloxone (Narcan, Nalone, Narcanti)

Drug Class: Opioid; a synthetic congener of oxymorphone.

Route of administration: Primarily intravenous, although naloxone may be administered intramuscularly or subcutaneously.

Naloxone has also been administered orally for nonsedating purposes (e.g., constipation).

Naloxone is metabolized in the liver, primarily by glucuronide conjugation. The drug is excreted in urine.

The pharmacokinetics of naloxone in newborns has been described [279–281].

Contraindications: Naloxone is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients.

Clinical application: Naloxone is an opioid antagonist. Its primary use in sedation is to reverse

sedation resulting from the administration of opioids such as fentanyl and morphine.

It is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine.

The American Academy of Pediatrics, Committee on Drugs issued guidelines on the use of naloxone in children in 1990 [282].

Another opioid antagonist, nalmefene, was approved in 1994. It differs from naloxone in that it has a longer duration of action. Because of its long half-life, it offers no advantage over naloxone, which remains the opioid antagonist of choice in the emergency room and areas of sedation.

Common adverse events include the following (in postoperative patients): Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone in postoperative patients may result in significant reversal of analgesia and may cause agitation. For patients in whom naloxone is administered for opioid depression, abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death.

Local Anesthetics

Lidocaine (Lignocaine)

Drug Class: Aminoethylamide.

Route of administration: Topical; also administered intravenously as an antiarrhythmic agent.

Lidocaine is metabolized in the liver through CYP450 enzymes [283].

The pharmacokinetics of lidocaine administered topically in children has been described [284–289].

Contraindication: Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.

Clinical application: Lidocaine has a wide range of clinical uses as a local anesthetic of intermediate duration. The combination of lidocaine (2.59%) and prilocaine (2.5%) in an occlusive dressing (EMLA Anesthetic Disc) is used as an anesthetic prior to venipuncture, skin graft harvesting, and infiltration of anesthetics into genitalia.

Common adverse events [290] are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy, or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature.

Central nervous system manifestations are excitatory and/or depressant and may be characterized by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, and respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or anaphylactoid reactions. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Neurologic adverse reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and

are also dependent upon the particular drug used, the route of administration, and the physical status of the patient.

Lidocaine hydrochloride injection should be employed only by physicians who are well versed in diagnosis and management of dose-related toxicity and other acute emergencies that might arise and then only after ensuring the immediate availability of oxygen, other resuscitative drugs, cardiopulmonary equipment, and the personnel needed for the proper management of toxic reactions and related emergencies. Delay in proper management of dose-related toxicity, underventilation from any cause, and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and, possibly, death.

Anti-Emetics

Ondansetron (Zofran)

Drug Class: Selective serotonin 5-HT3 receptor antagonist.

Route of administration: Intravenous.

Ondansetron is extensively metabolized, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by glucuronide or sulfate conjugation. In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP3A4 (predominantly), CYP1A2, and CYP2D6 [291].

The pharmacokinetics of ondansetron in children has been described [292–294].

Contraindication: Ondansetron is contraindicated for patients known to have hypersensitivity to the drug.

Clinical application: Ondansetron is administered for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, and the prevention of postoperative nausea and/or vomiting.

Common adverse events in pediatric patients are wound problems, anxiety or agitation, headache, drowsiness/sedation, pyrexia, bronchospasm, postprocedural pain, and diarrhea.

Metoclopramide (Maxolon, Reglan, Degan, Maxeran, Primperan, Pylomid, Cerucal, Pramin)

Drug Class: Dopaminergic blocking agent.

Route of administration: Intravenous.

Metoclopramide is rapidly and well absorbed. Peak plasma concentrations occur at about 1–2 h after a single oral dose. Similar time to peak is observed at steady state. The average elimination half-life in individuals with normal renal function is 5–6 h. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide. Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 h. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide. The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg), which suggests extensive distribution of drug to the tissues. Renal impairment affects the clearance of metoclopramide [295].

The pharmacokinetics of metoclopramide in children has been described [295–297].

Contraindications: Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

Clinical application: Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and

intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine, which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Common adverse events include restlessness, drowsiness, fatigue, and lassitude. Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation occur less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

Extrapyramidal reactions (EPS): Acute dystonic reactions, the most common type of EPS associated with metoclopramide, have been reported in a few patients treated with 30–40 mg of metoclopramide per day. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine. Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, and mask-like facies. Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance. Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, and foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Neuroleptic malignant syndrome: Rare occurrences of neuroleptic malignant syndrome have been reported. This potentially fatal syndrome is composed of the symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction.

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration.

Scopolamine (levo-duboisine, hyoscine)

Drug Class: Belladonna alkaloid.

Route of administration: Transdermal (at the postauricular area only).

Scopolamine's activity is due to the parent drug. The pharmacokinetics of scopolamine delivered via the system is due to the characteristics of both the drug and dosage form. The system is programmed to deliver in vivo approximately 1.0 mg of scopolamine at an approximately constant rate to the systemic circulation over 3 days.

Scopolamine is well absorbed percutaneously. Following application to the skin behind the ear, circulating plasma levels are detected within 4 h with peak levels being obtained, on average, within 24 h.

Although not well characterized, scopolamine is extensively metabolized and conjugated with less than 5% of the total dose appearing unchanged in the urine.

The pharmacokinetics of scopolamine administered transdermally in children has not been described.

Contraindications: Scopolamine is contraindicated in persons who are hypersensitive to the drug scopolamine or to other belladonna alkaloids, or to any ingredient or component in the formulation or delivery system, or in patients with angle-closure (narrow angle) glaucoma.

Clinical application: Scopolamine is indicated for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. The patch should be applied only to skin in the postauricular area.

The use of scopolamine in children is off-label [298].

Common adverse events include (for postoperative nausea and vomiting) dry mouth and dizziness.

Other adverse events reported include acute angle-closure (narrow-angle) glaucoma, confusion, difficulty urinating, dry, itchy, or conjunctival injection of eyes, restlessness, hallucinations, memory disturbances, rashes and erythema, and transient changes in heart rate.

Drug withdrawal/postremoval symptoms: Symptoms such as dizziness, nausea, vomiting, and headache occur following abrupt discontinuation of antimuscarinics. Similar symptoms, including disturbances of equilibrium, have been reported in some patients following discontinuation. These symptoms usually do not appear until 24 h or more after the patch has been removed. Some symptoms may be related to adaptation from a motion environment to a motion-free environment. More serious symptoms including muscle weakness, bradycardia, and hypotension may occur following discontinuation.

Diphenhydramine (Benadryl, DPH, DHM, Dimedrol, Daedalon)

Drug Class: Ethanolamine H_1-receptor antagonist.

Route of administration: Intravenous, oral.

Diphenhydramine in the injectable form has a rapid onset of action. It is widely distributed throughout the body, including the CNS. A portion of the drug is excreted unchanged in the urine, while the rest is metabolized via the liver.

The pharmacokinetics of diphenhydramine in children has been described [299].

Contraindications: Diphenhydramine should not be used in neonates or premature infants. Because of the higher risk of antihistamines for infants generally, and for neonates and prematures in particular, antihistamine therapy is contraindicated in nursing mothers.

Because of the risk of local necrosis, this drug should not be used as a local anesthetic.

Antihistamines are also contraindicated in the following conditions: Hypersensitivity to diphenhydramine hydrochloride and other antihistamines of similar chemical structure.

Clinical application: Diphenhydramine has significant anticholinergic and sedative effects that contribute to its efficacy as an antiemetic [300].

It is thought that the antiemetic properties of diphenhydramine are due to its ability to suppress motion-enhanced vestibular neuronal firing.

Common adverse events include diminished mental alertness, or, in the young pediatric patient, it causes excitation. Overdosage may cause hallucinations, convulsions, or death [301].

Dexamethasone

Drug Class: Steroid.

Route of administration: Intravenous.

The pharmacokinetics of dexamethasone in children has been described [302–304].

Contraindications: Dexamethasone is contraindicated in patients with systemic fungal infections and in patients who are hypersensitive to any components of this product.

Clinical application: Dexamethasone is a well-established antiemetic in patients receiving highly emetogenic cancer chemotherapy. Its antiemetic mechanism of action is not well understood, however.

Common adverse events include hypertension, weight gain, increased intraocular pressure, infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis [305].

Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

The adverse reactions that have been reported with dexamethasone or other corticosteroids encompass almost every system in the body such as allergic reactions, cardiovascular, dermatologic, endocrine, fluid and electrolyte disturbances, gastrointestinal, metabolic, musculoskeletal, neurological/psychiatric, and ophthalmic.

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Pharmacokinetics and Pharmacodynamics in the Pediatric Population

9

Brian J. Anderson

Introduction

Children still remain therapeutic orphans [1]. New regulations encouraging paediatric investigation of new drugs are rectifying this situation, but for many commonly used medicines the lack of well-conducted pharmacokinetic-pharmacodynamic (PK-PD) studies is replaced with extrapolation from adult or non-human data. While neonates, infants and children have different psychology, social structure, behaviour and disease spectrum from adults, they also share many similarities. Growth and developmental aspects account for major differences between neonates and infants and adults. However, once out of infancy, body size alone can account for many of the pharmacokinetic differences between children and adults. Pharmacodynamic factors that may influence response in early life remain poorly defined. Most PK and PD differences occur in the first few years of post-natal life with major changes occurring during the neonatal period that are mature by the end of infancy. Knowledge of paediatric PK-PD and of changes seen during growth and maturation is essential for dosing sedatives in children.

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PK Differences in the First Year of Life

Absorption

The rate at which most drugs are absorbed when given by the oral route is slower in neonates than in older children because gastric emptying is delayed and normal adult rates may not be reached until 6–8 months [2–5]. Slow gastric emptying and reduced clearance may dictate both reduced doses and reduced frequency of administration. This has been demonstrated for both cisapride [6] and acetaminophen [7]. Enteral administration through the rectum (e.g. thiopentone, methohexitone) takes approximately 8 min in children but is speedier for neonates undergoing cardiac catheter study or radiological sedation [8, 9].

The larger relative skin surface area, increased cutaneous perfusion and thinner stratum corneum in neonates [10] increase absorption and exposure of topically applied drugs (corticosteroids, local anaesthetic creams, antiseptics). Neonates have a tendency to form methaemoglobin because they have reduced levels of methaemoglobin reductase and foetal haemoglobin is more readily oxidised compared to adult haemoglobin. This, combined with increased absorption through the neonatal epidermis, resulted in reluctance to use lidocaine–prilocaine cream for repeated use in this age group [11, 12].

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Anaesthetic delivery to the alveoli is determined largely by alveolar ventilation and functional residual capacity (FRC). Neonates have increased alveolar ventilation. They also have a smaller FRC compared to adults because of increased chest wall compliance; this causes an increase in the speed of delivery. Pulmonary absorption is generally more rapid in infants and children than in adults [13]. The greater cardiac output and greater fraction of the cardiac output distributed to the vessel rich tissue group (i.e. a clearance factor) and the lower tissue/blood solubility (i.e. a volume factor) also effect the more rapid wash-in of inhalational anaesthetics in the younger age group [14]. Solubility determines volume of distribution. An inhalational agent with a greater volume of distribution will take longer to reach a steady-state concentration when delivered at a constant rate. The solubility in blood of halothane, isoflurane, enflurane and methoxyflurane are 18% less in neonates than in adults [15], attributable to altered serum albumin, globulin, cholesterol and triglyceride concentrations. The solubility of these same agents in the vessel-rich tissue group in neonates is approximately one half of that in adults [15]. The latter may be due to the greater water content and decreased protein and lipid concentration in neonatal tissues. Infants with their decreased solubility would be expected to have a shorter time to reach a predetermined F_E–F_I ratio because of a smaller volume of distribution. Age has little effect on the solubility of the less soluble agents, nitrous oxide and sevoflurane [16].

Induction of anaesthesia may be slowed by right-to-left shunting of blood in neonates suffering cyanotic congenital cardiac disease or intrapulmonary conditions. This slowing is greatest with the least soluble anaesthetics [17]. Left to right shunts usually have minimal impact on uptake because cardiac output is increased so that systemic tissue perfusion is maintained at normal levels. The flow of mixed venous blood returning to the right heart ready for anaesthetic uptake is normal. If cardiac output is not increased and peripheral perfusion is reduced, then there will be less anaesthetic uptake in the lung. Although alveolar anaesthetic partial pressure may be observed to rise rapidly, there is a slower rise in tissue partial pressure and anaesthetic effect is delayed.

Bioavailability

The oral bioavailability may be affected by interactions with food when feeding is frequent in the neonate (e.g. phenytoin [18]), use of adult formulations that are divided or altered for paediatric use (nizatidine [19]) and by lower cytochrome P450 enzyme activity in the intestine. The latter may cause an increased bioavailability of midazolam because CYP3A activity is reduced [20]. The use of adult vials for paediatric use may result in dose inaccuracy, causing a relative increase or decrease in assumed bioavailability [21].

The frequent passage of stools in the neonate may render suppository use ineffective. Variable absorption and bioavailability have resulted in respiratory arrest when repeat opioids are administered through the rectal route to children [22].

Distribution

Body Composition

Total body water and extracellular fluid (ECF) [23] are increased in neonates and reduction tends to follow post-natal age (PNA). Polar drugs such as the non-depolarising neuromuscular blocking drugs (NMBDs) and aminoglycosides distribute rapidly into the ECF, but enter cells more slowly. The initial dose of such drugs is consequently higher in the neonate compared to the infant, older child or adult.

The percentage of body weight contributed by fat is 3% in a 1.5-kg premature neonate and 12% in a term neonate; this proportion doubles by 4–5 months of age. “Baby fat” is lost when infants start walking and protein mass increases (20% in a term neonate, 50% in an adult). These body-component changes affect volumes of distribution of drugs. Volume of distribution influences initial dose estimates. Fentanyl has an increased volume of distribution in neonates. The volume of distribution at steady-state is 5.9 (SD 1.5) L/kg in a neonate under 1 month of age compared

to 1.6 (SD 0.3) L/kg in an adult [24]. This may contribute to the reduced degree of respiratory depression seen after single doses as high as 10 μg/kg in older term neonates.

Reduction of propofol concentrations after induction is attributable to redistribution rather than rapid clearance. Neonates have low body fat and muscle content, and so less propofol is apportioned to these tissues. Delayed awakening occurs because CNS concentration remains higher than that observed in older children as a consequence of reduced redistribution.

Plasma Proteins

Albumen and alpha-1 acid glycoprotein (AAG) concentrations are reduced in neonates but are similar to those in adults by 6 months, although between-patient variability is high (0.32–0.92 g/L) [25, 26]. AAG is an acute phase reactant that increases after surgical stress. This causes an increase in total plasma concentrations for low to intermediate extraction drugs such as bupivacaine [27]. The unbound concentration, however, will not change because clearance of the unbound drug is affected only by the intrinsic metabolising capacity of the liver. Any increase in unbound concentrations observed during long-term epidural is attributable to reduced clearance rather than AAG concentration [28].

Plasma albumin concentrations are lowest in premature infants, and other foetal proteins such as alpha-fetoprotein (synthesised by the embryonic yolk sac, foetal gastrointestinal tract and liver that has 40% homology with albumin) have reduced affinity for drugs. In addition, increased concentrations of free fatty acids and unconjugated bilirubin compete with acidic drugs for albumin binding sites. Neonates also have a tendency to manifest a metabolic acidosis that alters ionisation and binding properties of plasma proteins. Serum albumin concentrations approximate adult values by 5 months of age and binding capacity approaches adult values by 1 year of age. The induction dose of thiopentone is lower in neonates than older children. It is possible that this is related to decreased binding of thiopentone to plasma albumin; 13% of the drug is unbound in newborns compared to 7% in adults [29].

Regional Blood Flows

The initial phase of distribution after intravenous administration reflects regional blood flow. Consequently, the brain, heart and liver are the tissues first exposed to the drug. The drug is then redistributed to other relatively well-perfused tissues, such as skeletal muscle. There is a much slower tertiary distribution to relatively underperfused tissues of the body that is noted with long-term drug infusions.

Apart from the neonatal circulatory changes that occur at birth (e.g. secondary to functional closure of the ductus venosus and ductus arteriosus), there are differences in relative organ mass and regional blood flow change with growth and development during the first few months of life. Blood flow, relative to cardiac output, to the kidney and brain increases, while that to the liver decreases through the neonatal period [30]. Cerebral and hepatic mass as a proportion of body weight are much higher in the infant than in the adult [31].

Mean cerebral blood flow is highest in early childhood (70 mL/min/100 g) at about 3–8 years of age [32]. It is reduced before this age in neonates and later in adults, where flows are similar (50 mL/min/100 g) [33]. The highly lipophilic induction agents diffuse rapidly across the blood-brain barrier (BBB) to achieve concentration equilibrium with brain tissue. Reduced cardiac output in neonates and reduced cerebral perfusion means that onset time after intravenous induction is slower in neonates that in early childhood. Offset time is also delayed because redistribution to the well-perfused and deep, underperfused tissues is less.

Blood–Brain Barrier (BBB)

The BBB is an elaborate network of complex tight junctions between specialised endothelial cells that restricts the paracellular diffusion of hydrophilic molecules from the blood to the brain substance. Confusion over the importance of this barrier in the neonate exists, partly because of early studies comparing respiratory depression caused by the opioids, morphine and pethidine. Greater respiratory depression was evident in neonates after morphine given as an adult equipotent

dose of pethidine [34]. This finding is consistent with pethidine, unlike morphine, being lipid soluble and, therefore, crossing the immature or mature BBB equally [34]. However, plasma opioid concentrations were not measured in that study, and the increased neonatal respiratory depression observed after morphine could be due to reduced volume of distribution of morphine in term neonates 1–4 days (1.3 L/kg) compared to those at 8–60 days (1.8 L/kg) 61–180 days (2.4 L/kg) and adults (2.8 L/kg) [35]. Consequently, we might expect initial concentrations of morphine to be higher in neonates than in adults and consequent respiratory depression greater. Respiratory depression, as measured by carbon dioxide response curves or by arterial oxygen tension, is similar in children from 2 to 570 days of age at the same morphine concentration [36].

The BBB may have an impact in other ways. There are specific transport systems selectively expressed in the barrier endothelial cell membranes that mediate the transport of nutrients into the CNS and of toxic metabolites out of the CNS. Small molecules access foetal and neonatal brains more readily than they do adult brains [37]. BBB function improves gradually throughout foetal brain development, possibly reaching maturity at term [37]. Kernicterus, for example, is more common in the premature neonate than the term neonate. Pathological conditions within the CNS can cause BBB breakdown or alterations in transport systems play an important role in the pathogenesis of many CNS diseases. Proinflammatory substances and specific disease-associated proteins often mediate BBB dysfunction [38].

Fentanyl is actively transported across the BBB by a saturable ATP-dependent process, while ATP-binding cassette proteins such as P-glycoprotein actively pump out opioids such as fentanyl and morphine [39]. P-glycoprotein modulation significantly influences opioid brain distribution and onset time, magnitude and duration of analgesic response [40]. Modulation may occur during disease processes, increased temperature, or other substances (e.g. verapamil, magnesium) [39]. Genetic polymorphisms affecting P-glycoprotein-related genes may explain some individual differences in CNS-active drug sensitivity [41].

Drug Metabolism

The main routes through which drugs and their metabolites leave the body are the hepatobiliary system, the kidneys and the lungs. The liver is the primary organ for clearance of most drugs, although the lungs have a major role for anaesthetic vapours. Non-polar, lipid-soluble drugs are converted to more polar and water soluble compounds. Water soluble drugs and metabolites rendered water soluble by the liver are excreted by the kidneys. Both hepatic and renal systems are immature in the neonate and mature within the first year of life. The impact of birth as an accelerator or temporal switch in the maturation of these processes remains uncertain. Maturation of these processes is commonly measured against post-menstrual age (PMA), although PNA may also have impact [42, 43] on maturation and longitudinal PK studies are required to distinguish the separate influences of these two age types.

Descriptors for Metabolism Maturation

Three descriptors (size, maturation and organ function [OF]) have been used to describe changes in clearance with age [44, 45]. Size is commonly standardised using body surface area (BSA), although in all species studied, including humans, the log of basal metabolic rate (BMR) plotted against the log of body weight produces a straight line with a slope of 3/4. This is different to the BSA exponent of 2/3. Fractal geometry is used to mathematically explain this phenomenon [46]. A great many physiological, structural and time-related variables scale predictably within and between species with weight (W) exponents (PWR) of 3/4, 1 and 1/4 respectively [45].

These exponents have applicability to pharmacokinetic parameters such as clearance (CL), volume (V) and half-time [45]. The factor for size (F_{size}) for total drug clearance may be expected to scale weight with an exponent of 3/4:

$$F_{size} = \left(\frac{W}{70}\right)^{3/4}.$$

Remifentanil clearance in children 1 month to 9 years is similar to adult rates when scaled using an allometric exponent of 3/4 [47]. Remifentanil

is hydrolysed by non-specific tissue and plasma esterases that do not appear to be influenced by age after scaling for size.

The effect of size on the dose of remifentanil tolerated during spontaneous ventilation under anaesthesia has been investigated in children undergoing strabismus surgery ($n=45$, age 6 months to 9 years). The propofol infusion was titrated using state entropy as a pharmacodynamic end point and remifentanil infused, using a modified up-and-down method, with respiratory rate depression as a pharmacodynamic end point. A respiratory rate of just greater than 10, stable for 10 min, determined the final remifentanil infusion rate [48]. This influence of age on the remifentanil infusion requirement is shown in Fig. 9.1. Superimposed on this figure are clearance estimates for age, determined by size using an allometric model with a standardised clearance of 2,790 mL/min for a 70 kg person. Clearance mirrors infusion rate in children over the age of 1 year. There is a divergence between clearance estimate and infusion rate in those children in infancy. The higher infusion rates recorded in those infants can be attributed to greater suppression of respiratory drive in this age group than the older children during the study; a respiratory rate of 10 breaths/min in an infant is disproportionately slow compared to the same rate in a 7-year-old child, suggesting excessive dose.

For most drugs, however, allometry alone is insufficient to predict clearance in neonates and infants from adult estimates. The addition of a model describing maturation with age is required. The sigmoid hyperbolic function (also known as the Hill equation) [49] has also been found useful for describing this maturation process (MF).

$$\mathrm{MF} = \frac{\mathrm{PMA}^{\mathrm{Hill}}}{\mathrm{TM}_{50}^{\mathrm{Hill}} + \mathrm{PMA}^{\mathrm{Hill}}}.$$

The TM_{50} describes the maturation half-time, while the Hill coefficient relates to the slope of this maturation profile. The maturation profile for dexmedetomidine expressed using allometric scaling, and this maturation model is shown in Fig. 9.2.

OF remains the other major covariate influence on clearance. While renal pathology may be reflected by assessment such as creatinine clearance, distinguishing this from normal physiology in infants may be difficult unless ordinary renal maturation is understood [44]. Although specific organ dysfunction of the kidney or liver are well

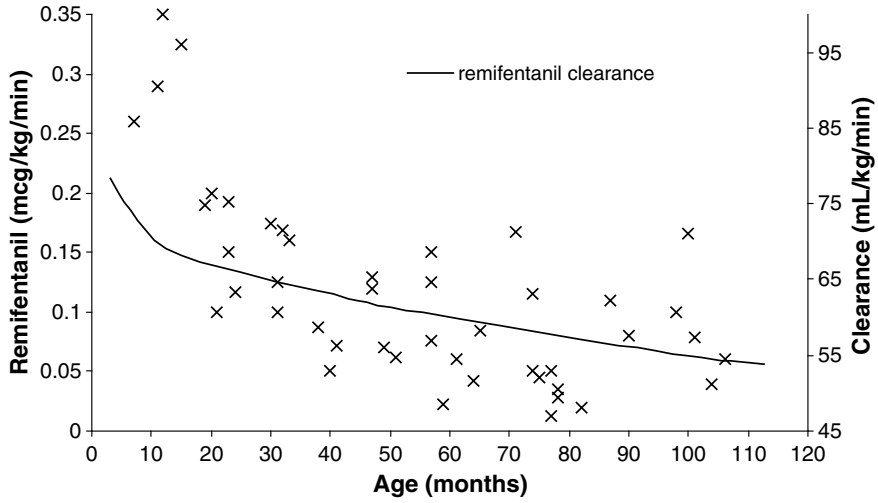

Fig. 9.1 The effect of age on the dose of remifentanil tolerated during spontaneous ventilation under anaesthesia in children undergoing strabismus surgery [48]. Superimposed on this plot is estimated remifentanil clearance determined using an allometric model [151]. There is a mismatch between clearance and infusion rate for those individuals still in infancy (from Anderson [150] with permission from Wiley-Blackwell)

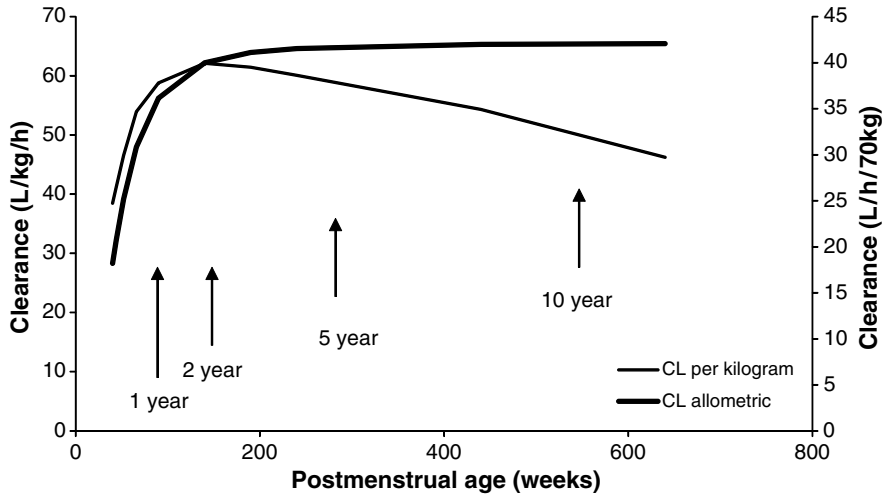

Fig. 9.2 Dexmedetomidine clearance changes with age, expressed both as per kilogram and using allometric scaling with a maturation model. The per kilogram model (L/h/kg) demonstrates an increased clearance in infants that explains the observed increased infusion (mg/min/kg) required for sedation in this age group. Use of the allometric model allows better understanding of the clearance maturation process. Data from Potts et al. [152]

recognised as having effect on clearance, other processes (sepsis, malnutrition, disease severity scores) can also be used as markers of reduced clearance.

Pharmacokinetic parameters (P) can be described in an individual as the product of size (F_{size}), maturation (MF) and OF influences where P_{std} is the value in a standard size adult without pathological changes in OF:

$$P = P_{std} \cdot F_{size} \cdot \text{MF} \cdot \text{OF}.$$

Hepatic Elimination

Phase 1

The mixed-function P450 oxidases are reduced in neonates [50, 51]. CYP2E1 activity surges after birth [52], CYP2D6 becomes detectable soon thereafter CYP3A4 and CYP2C family appear during the first week, whereas CYP1A2 is the last to appear [53]. Neonates are dependent on the immature CYP3A4 for levobupivacaine clearance and CYP1A2 for ropivacaine clearance, dictating reduced epidural infusion rates in this age group [54–56].

If a drug has a high extraction ratio then intrinsic clearance may be very much greater than liver blood flow and in these situations hepatic clearance is primarily determined by liver blood flow characteristics. Fentanyl clearance (CYP3A4) is 70–80% of adult values in term neonates and, standardised to a 70-kg person, reaches adult values within the first few weeks of life [28]. Omphalocele repair may be associated with raised intraabdominal pressure (an OF effect), resulting in reduced fentanyl clearance attributable to decreased hepatic blood flow.

Phase 2

Some phase II pathways are mature in term neonates at birth (sulphate conjugation), while others are not (acetylation, glycination, glucuronidation) [57]. Allometric body-size scaling complemented by maturation models [45, 58] have been used to unravel the developmental PK of morphine [59, 60] and paracetamol [61, 62]. Paracetamol and morphine are cleared by individual isoforms of glucuronosyl transferase (UGT1A6 and UGT2B7), as is bilirubin (UGT1A1). Clearance of both drugs is immature in the premature 24 week PMA neonate and mature to reach adult rates by the first year of life. Dexmedetomidine is also cleared predominantly by the UGT system and has a similar maturation

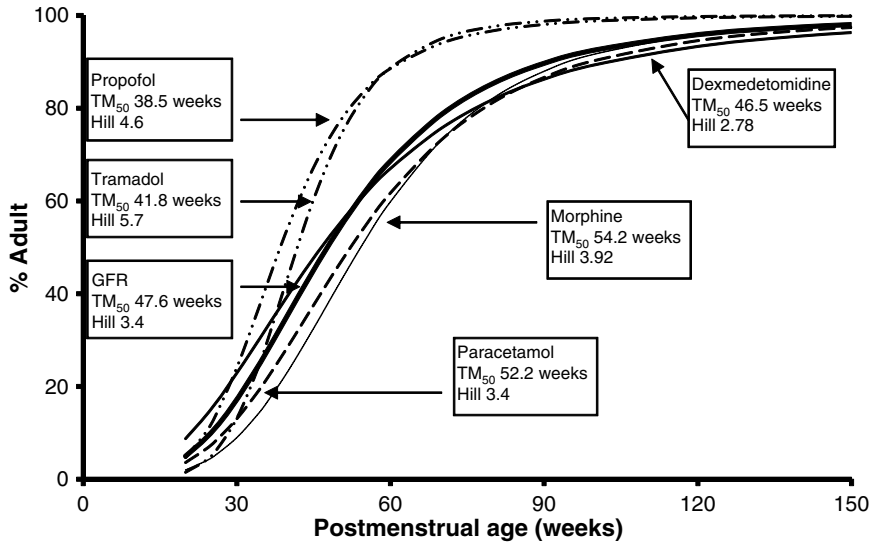

Fig. 9.3 Clearance maturation, expressed as a percentage of mature clearance, of drugs where glucuronide conjugation (paracetamol, morphine, dexmedetomidine) plays a major role. These profiles are closely aligned with Glomerular filtration rate (GFR). By contrast, cytochrome P450 isoenzymes also contribute to propofol metabolism and cause a faster maturation profile than expected from glucuronide conjugation alone. Tramadol clearance maturation (Phase I, CYP2D6, CYP3A) is also rapid. Maturation parameter estimates were taken from refs. [58, 60, 63, 69, 75, 153]

profile [63]. Glucuronidation is also the major metabolic pathway of propofol metabolism, although multiple cytochrome P450 isoenzymes, including CYP2B6, CYP2C9 or CYP2A6, contribute to its metabolism and cause a faster maturation profile (Fig. 9.3) than expected from glucuronide conjugation alone [43].

The impact of OF has been demonstrated on morphine clearance. Clearance is greater in infants undergoing non-cardiac surgery than in those undergoing cardiac surgery [64], or in those receiving extracorporeal membrane oxygenation [65] or positive pressure ventilation [60]. Similarly, clearance of propofol was reduced after cardiac surgery in children admitted to a paediatric intensive care [66]. A circadian night rhythm effect was noted in an investigation of infant propofol sedation after major craniofacial surgery [67].

Renal Elimination

Drugs and their metabolites are excreted by the kidneys by two processes – glomerular filtration and tubular secretion that mature at different rates [68]. Glomerular filtration rate (GFR) is only 10% that of mature value at 25 weeks, 35% at term and 90% of the adult GFR at 1 year of age [69]. Tubular secretion maturation lags behind that of GFR [68]. Aminoglycosides are almost exclusively cleared by renal elimination and maintenance dose is predicted by PMA because it predicts the time course of development of renal function [70]. The clearance of the old NMBD, d-tubocurare, can be directly correlated with GFR [71].

Immaturity of clearance pathways can be used to our advantage when managing apnoea after anaesthesia in the premature nursery graduate. N_7-methylation of theophylline in the newborn to produce caffeine is well developed, whereas oxidative demethylation (CYP1A2) responsible for caffeine metabolism is deficient and develops over the ensuing months. Theophylline is effective for the management of post-operative apnoea in the premature neonate, partly because it is a prodrug of caffeine, which is effective controlling apnoea. Caffeine can only be slowly cleared by the immature kidney.

Pulmonary Elimination

The factors determining anaesthetic absorption (alveolar ventilation, FRC, cardiac output, tissue/

blood solubility) also contribute to elimination. We might anticipate more rapid wash-out in neonates than adults for any given duration of anaesthesia because there is less distribution to fat and muscle content. The greater decrease in cardiac output induced by halothane in neonates might be expected to speed elimination, but brain perfusion will also be reduced and this slows recovery. Halothane, in particular, and to a far lesser extent isoflurane and sevoflurane undergo hepatic metabolism, but contribution is small compared to pulmonary elimination [72].

Metabolites

Many drugs have active metabolites that contribute to effect. Examples include norketamine from ketamine [73], 4′-hydroxydiclofenac from diclofenac [74], *O*-demethyl tramadol from tramadol [75], hydroxymidazolam from midazolam [76] and morphine 6-glucuronide (M6G) from morphine [59].

Contributions to both the desired effect (analgesia) and the undesired effects (nausea, respiratory depression) of M6G are the subject of clinical controversy [77]. M6G has been explored in adults using pupil size as a measure of central opioid effect, but results are confusing. Effect compartment modelling suggested that M6G was apparently 22 times less potent than morphine [78, 79]. Contrarily, other authors have suggested that M6G was 4 times more potent than morphine in producing meiosis [80], half as potent as an analgesic [81] and with reduced respiratory depressive effects [82]. The relative ratios of morphine to M6G vary in neonates and early infancy, depending on relative maturation of UGT2B7 (formation of M6G) and GFR (elimination of M6G). Term neonates less than 7 days old have a lower ratio of plasma morphine/M6G than those over 1 year despite similar doses [83]. The impact of this is uncertain.

Pharmacogenomics

Pharmacogenomics (PGs) is the investigation of variations of DNA and RNA characteristics as related to drug response that incorporates both PK and PD. There is large between individual PK variability that is contributed to by polymorphisms of the genes encoding for metabolic enzymes [84]. Genetic variability influencing plasma cholinesterase activity and its influence on succinylcholine is a well-known example. Another example is the CYP2D6 single nuclear polymorphism (SNP) that is inherited as an autosomal recessive trait. Homozygous individuals are deficient in the metabolism of a variety of important groups of drugs – β-adrenoreceptor blocking agents, antidepressants, neuroleptic agents and opioids. Poor metabolisers have reduced morphine production from codeine [85, 86]. Tramadol is also metabolised by *O*-demethylation in the liver (CYP2D6) to *O*-desmethyl tramadol (M1) and the M1 metabolite has a mu-opioid affinity approximately 200 times greater than tramadol.

A SNP may only be important if it contributes greater than 50% metabolism, has an active metabolite, a steep dose–response relationship and a narrow therapeutic index. These polymorphisms may have little impact during the neonatal period when metabolism is developmentally limited [6, 75, 87–89]. SNPs will certainly have impact in infants and children. Impact will be dependent on the rate of maturation of the specific enzyme system.

PG differences also have impact on PD. Candidate genes involved in pain perception, pain processing and pain management such as opioid receptors, transporters and other targets of pharmacotherapy are under investigation. Genetic differences (G118 allele) may explain why some patients need higher opioid doses and the adverse effects profile may be modified by these mutations [90]. Some genes (e.g. foetal haemoglobin) are expressed much more in early life than in adults, and gene switching may mean that a drug is effective at one age and not another.

In adults, gene testing may prove valuable for reducing adverse drug effects [91, 92]. However, most drug responses involve a large number of proteins regulated by multiple genes. Genotype does not equate with phenotype; environment, concomitant therapy and disease have impact, and allele prevalence varies among ethnic groups.

The situation in children is more complex. Allelic variants may remain unchanged throughout life but transcriptomonic, proteomic and metobonomic data in children are continuously changing throughout development.

PD Differences in the First Year of Life

Children's responses to drugs have much in common with the responses in adults [93]. The perception that drug effects differ in children arises because the drugs have not been adequately studied in paediatric populations who have size and maturation related effects as well as different diseases. Neonates and infant, however, often have altered pharmacodynamics.

The minimal alveolar concentration (MAC) for almost all anaesthetic vapours is less in neonates than in infancy, which is in turn greater than that observed in children and adults [14]. MAC of isoflurane in preterm neonates less than 32 weeks gestation was 1.28%, and MAC in neonates 32–37 weeks gestation was 1.41% [94]. This value rose to 1.87% by 6 months before decreasing again over childhood [94]. The cause of these differences is uncertain and may relate to maturation changes in cerebral blood flow, gamma-aminobutyric acid ($GABA_A$) receptor numbers or developmental shifts in the regulation of chloride transporters.

Neonates have an increased sensitivity to the effects of NMBDs [71]. The reason for this is unknown, but it is consistent with the observation that there is a threefold reduction in the release of acetylcholine from the infant rat phrenic nerve [95, 96]. The increased volume of distribution, however, means that a single NMBD dose is the same as that in the older child; reduced clearance prolongs duration.

Cardiac calcium stores in the endoplasmic reticulum are reduced in the neonatal heart because of immaturity. Exogenous calcium has greater impact on contractility in this age group than in older children or adults. There are some data to suggest greater sensitivity to warfarin in children, but the mechanism is not determined [97]. Amide local anaesthetic agents induce shorter block duration and require a larger weight scaled dose to achieve similar dermatomal levels when given by subarachnoid block to infants. This may be due, in part, to myelination, spacing of nodes of Ranvier, and length of nerve exposed as well as size factors. There is an age-dependent expression of intestinal motilin receptors and the modulation of gastric antral contractions in neonates. Prokinetic agents may not be useful in very preterm infants, partially useful in older preterm infants, and useful in full-term infants. Similarly, bronchodilators in infants are ineffective because of the paucity of bronchial smooth muscle that can cause bronchospasm.

Measurement of PD End Points

Outcome measures are more difficult to assess in neonates and infants than in children or adults. Measurement techniques, disease and pathology differences, inhomogeneous groups, recruitment issues, ethical considerations and end-point definition for establishing efficacy and safety confuse data interpretation [98].

Common effects measured include anaesthesia depth, pain and sedation and neuromuscular blockade. A common effect measure used to assess depth of anaesthesia is the electroencephalogram or a modification of detected EEG signals (spectral edge frequency, bispectral index, entropy). Physiological studies in adults and children indicate that EEG-derived anaesthesia depth monitors can provide an imprecise and drug-dependent measure of arousal. Although the outputs from these monitors do not closely represent any true physiological entity, they can be used as guides for anaesthesia and in so doing have improved outcomes in adults. In older children, the physiology, anatomy and clinical observations indicate that the performance of the monitors may be similar to that in adults. In infants, their use cannot be supported yet in theory or in practice [99, 100]. During anaesthesia, the EEG in infants is fundamentally different from the EEG in older children; there remains a need for specific neonate-derived algorithms if

EEG-derived anaesthesia depth monitors are to be used in neonates [101, 102].

The Children's Hospital of Wisconsin Sedation Scale [103] has been used to investigate ketamine in the emergency department [104]. However, despite the use of such scales in procedural pain or sedation studies, few behavioural scales have been adequately validated in this setting [105, 106]. Inter-observer variability can be high [107]. Most scores are validated for the acute, procedural setting and perform less for subacute or chronic pain or stress.

Population Modelling

Models describe systems in simple terms, although some models may be quite sophisticated. They are used to describe, predict and explain observations. Pharmacokinetic (PK) and pharmacodynamic (PD) models are used to improve paediatric anaesthetic and sedation management. They quantify the exposure–response relationship, often providing clarity and insight into complex systems as well as a mechanistic understanding of the drug effect. Dose selection can be rationalised. Models may enable extrapolation beyond observed data. Modelling is a knowledge management tool; it captures and integrates data from all studies. Models can also be used for hypothesis testing and can drive decision-making during drug development.

Population PK and PD modelling using nonlinear mixed effects models has had enormous impact in adult anaesthetic pharmacology. This methodology has particular applicability in children where the blood volume available for sampling is limited. Sparse data from multiple subjects can be used. Sampling times are not crucial for population methods and can be fitted around clinical procedures or outpatient appointments. Sampling time bands rather than exact times are equally effective and allow flexibility in neonates. Sampling cannulae for PK studies may become obstructed, parents may refuse repeat sampling and repeat venepuncture is frowned upon. Missing data, however, can still be used in a paediatric population analysis. Data from different studies can be pooled [108, 109].

The Target Concentration Approach

The goal of treatment is the target effect. A pharmacodynamic model is used to predict the target concentration given a target effect. Population estimates for the PD model parameters and covariate information are used to predict typical PD values in a specific patient. Population estimates of PK model parameters estimates and covariate information are then used to predict typical PK values in a typical patient. For example, a dexmedetomidine steady-state target concentration of 0.6 μg/L may be achieved with an infusion of 0.33 μg/kg/h in a neonate, 0.51 μg/kg/h in a 1-year-old and 0.47 μg/kg/h in an 8-year-old [63]. This target concentration strategy is a powerful tool for determining clinical dose [110]. Monitoring of serum drug concentrations and Bayesian forecasting may be used to improve dosing in individual patients.

This target effect approach is intrinsic to paediatric anaesthesiologists using target controlled infusion (TCI) systems. These devices target a specific plasma or effect site concentration in a typical individual, and this concentration is assumed to have a typical target effect. The target concentration is one that achieves target therapeutic effect (e.g. anaesthesia) without excessive adverse effects (e.g. hypotension). Effect monitoring (e.g. Bispectral index, BIS) can be used to refine the target effect.

Pharmacokinetic Models

Compartment models dominate the anaesthetic literature. Standard compartment models may be unable to accurately describe drug concentrations immediately after bolus administration of an anaesthetic induction agent because mixing in the central compartment is not instantaneous, making it difficult to model the fast blood-to-brain concentration equilibrium [111] and pulmonary uptake may also occur [112]. Recirculatory models help explain these early phase PK [113]. Such models have proved valuable determining anaesthetic induction doses [114] and NMBD pharmacodynamics [115]. Physiologically based pharmacokinetic (PBPK) modelling has been used to assist with first-time dosing in children. A general PBPK model for drug disposition in infants and children,

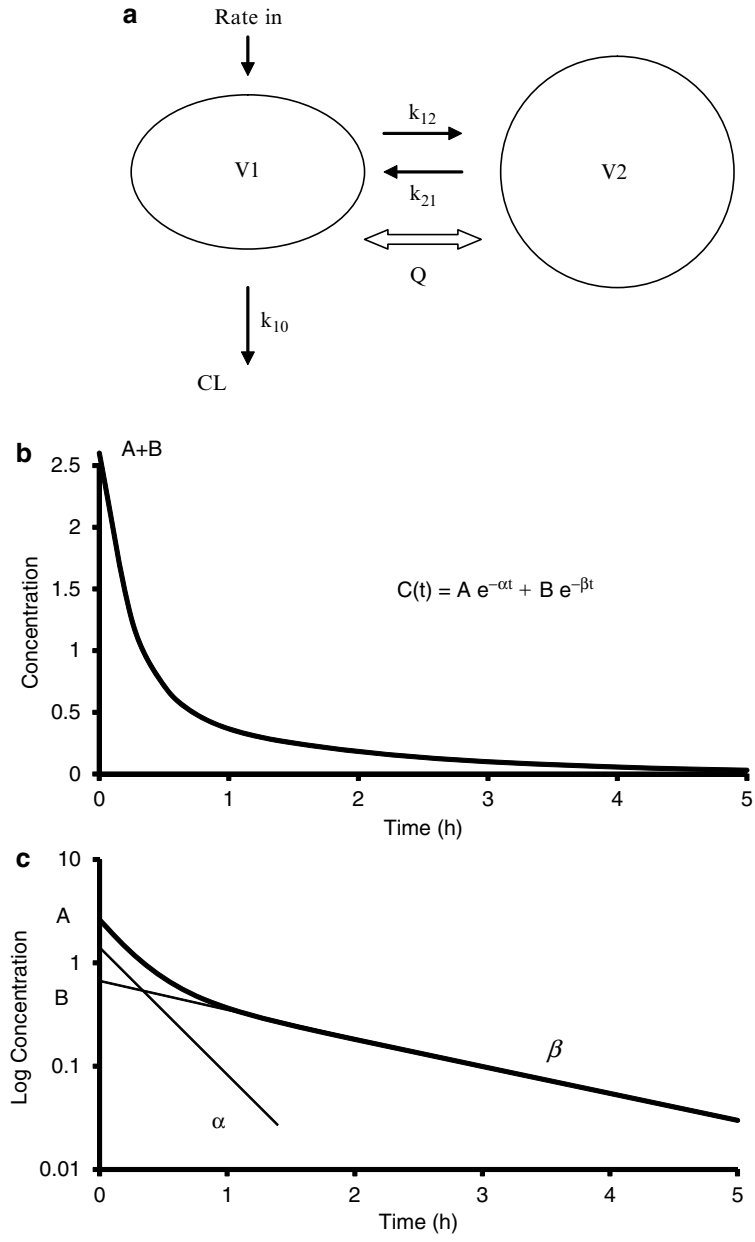

Fig. 9.4 (**a**) A mammillary two-compartment PK model. (**b**) Time–concentration profile for a two-compartment model. (**c**) Conversion of concentration to a log scale allows estimation of elimination constants and compartment volumes

covering the age range from birth to adulthood, has been successfully evaluated using theophylline and midazolam as model drugs [30].

A single compartment is often insufficient to characterise the time–concentration profile and further compartments are required (mammillary models). Drug is administered into a central compartment (V_1) and redistributes to peripheral compartments (V_2, V_3, etc., Fig. 9.4a). In a two compartment model transfer of drug between the central and peripheral compartment is relatively fast compared with the rate of elimination. A plot of the natural log of concentration after bolus reveals two distinct slopes (rate constants, *a* and *b*, Fig. 9.4b). Consequently, the time–concentration profile is commonly described using a polyexponential function.

$$C(t) = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}.$$

These polyexponential parameters have little connection with underlying physiology and an alternative parameterisation is the use of a central volume and three rate constants (k_{10}, k_{12}, k_{21}) that describe drug distribution between compartments. Another common method is to use two volumes (V_1, V_2) and two clearances (CL, Q). Q is the inter-compartment clearance.

Students are commonly taught to estimate compartment model PK parameters through interpretation of graphs representing time–concentration profiles. Conversion of concentration to a log scale allows estimation of elimination constants and compartment volumes (Fig. 9.4c). Integration of the function describing this profile yields an AUC (area under the curve), from which CL can be determined

$$CL = \frac{Dose}{AUC}.$$

Computers have enabled the use of non-linear regression to directly estimate parameters through iterative techniques using least squares curve fitting. Models with two or more compartments are now commonly solved using differential equations.

Parameter estimates (CL, Q, V_1, V_2) can be used to predict dose. A loading dose raises concentration in the plasma to target concentration promptly and may be desirable in anaesthesia when rapid effect is required. In a one-compartment model, the volume of distribution is the proportionality factor that relates total amount of drug in the body to plasma concentration (TC = target concentration)

$$\text{Loading dose} = V \cdot TC.$$

This calculation may not be applicable to many sedative drugs that are characterised using multi-compartment models. The use of V_1 results in a loading dose too high; too high a dose may cause transient toxicity.

An alternative technique is to use the target effect dose. The time to peak effect (T_{peak}) is dependent on clearance and effect site equilibration half-time ($T_{1/2keo}$). At a submaximal dose, T_{peak} is independent of dose. At supramaximal doses, maximal effect will occur earlier than T_{peak} and persist for longer duration. The T_{peak} concept has been used to calculate optimal initial bolus doses [116].

Clearance is the most important parameter when defining a rational steady-state dosage regimen. At steady state

$$\text{Dosing rate}_{ss} = \text{rate of elimination}_{ss} = CL \cdot TC.$$

When a drug is given intermittently

$$\text{Maintenance dose} = \text{dosing rate} \times \text{dosing interval}$$

When a drug is given by constant infusion

$$\text{Infusion rate}_{ss} = \text{dosing rate}_{ss}.$$

Once the target concentration of a drug is defined, the infusion rate is determined by CL at steady state. Many sedative drugs distribute to peripheral compartments, and steady state may not be achieved during the time of infusion. Dose adjustment is required to achieve constant effect until steady-state conditions are reached.

Propofol PK are usually described using a three-compartment mammillary model. In order to achieve steady state 3 μg/mL in children of 3–11 years, dosing changes are required, e.g. a loading dose of 2.5 mg/kg followed by an infusion rate of 15 mg/kg/h for the first 15 min, 13 mg/kg/h from 15 to 30 min, 11 mg/kg/h from 30 to 60 min, 10 mg/kg/h from 1 to 2 h and 9 mg/kg/h from 2 to 4 h. TCI pumps are capable of finer-tuning by making adjustments at 10 s intervals [117].

The PK of drug disposition confined to a one-compartment model is often expressed in terms of half-life. Half-life ($T_{1/2}$) is the time required to change the amount of drug in a body compartment by one half.

$$T_{1/2} = \ln(2) \cdot \frac{V}{CL}.$$

This half-life is related to the elimination rate constant (k), a parameter representing the slope of the exponential decay curve.

$$k = \frac{CL}{V}.$$

Elimination half-life is of no value in characterising disposition of intravenous anaesthetic drugs with multiple compartments during dosing periods relevant to anaesthesia. A more useful concept is that of the context-sensitive half-time

where "context" refers to infusion duration. This is the time required for the plasma drug concentration to decline by 50% after terminating infusion [118]. The context-sensitive half-time is the same as the elimination half-life for a one-compartment model and does not change with infusion duration.

Context-sensitive half-time may be independent of infusion duration (e.g. remifentanil 2.5 min); moderately affected (propofol 12 min at 1 h, 38 min at 8 h); or display marked prolongation (e.g. fentanyl 1 h at 24 min, 8 h at 280 min). This is due to return of drug to plasma from peripheral compartments after ceasing infusion. Peripheral compartment size differs in children from adults so that at termination of infusion more drug may remain in the body for any given plasma concentration than in adults. The context-sensitive half-time for children given propofol, for example, is longer [117]. The context-sensitive half-time gives an insight into the PK of a hypnotic drug, but the parameter may not be clinically relevant because the percentage decrease in concentration required for recovery is not necessarily 50%.

Pharmacodynamic Models

Pharmacokinetics is what the body does to the drug, while pharmacodynamics is what the drug does to the body. The precise boundary between these two processes is ill defined and often requires a link describing movement of drug from the plasma to the effect site and its target. Drugs may exert effect at non-specific membrane sites, by interference with transport mechanisms, by enzyme inhibition or induction or by activation or inhibition of receptors.

The Sigmoid E_{max} Model

The relation between drug concentration and effect may be described by the Hill equation (see maturation model above), well known to anaesthesiologists through the oxygen dissociation curve [49], according to the equation

$$\text{Effect} = \text{E}_0 + \frac{(\text{E}_{max} \cdot \text{Ce}^{\text{N}})}{(\text{EC}_{50}^{\text{N}} + \text{Ce}^{\text{N}})},$$

where E_0 is the baseline response, E_{max} is the maximum effect change, Ce is the concentration in the effect compartment, EC_{50} is the concentration producing 50% E_{max} and N is the Hill coefficient defining the steepness of the concentration–response curve. Efficacy is the maximum response on a dose or concentration–response curve. EC_{50} can be considered a measure of potency relative to another drug provided N and E_{max} for the two drugs are the same. A concentration–response relationship for acetaminophen has been described using this model. An EC_{50} of 9.8 mg/L, $N = 1$ and an E_{max} of 5.3 pain units (VAS 0–10) was reported [119]. Midazolam PD in adults have been similarly defined using EEG response [120, 121].

Quantal Effect Model

The potency of anaesthetic vapours may be expressed by MAC and this is the concentration at which 50% of subjects move in response to a standard surgical stimulus. MAC appears at first sight to be similar to EC_{50}, but is an expression of quantal response rather than magnitude of effect. There are two methods of estimating MAC. Responses can be recorded over the clinical dose range in a large number of subjects and logistic regression applied to estimate the relationship between dose and quantal effect; the MAC can then be interpolated. Large numbers of subjects may not be available, and so an alternative is often used. The "up-and-down" method described by Dixon [122, 123] estimates only the MAC rather than the entire sigmoid curve. It involves a study of only one concentration in each subject and, in a sequence of subjects, each receives a concentration depending upon the response of the previous subject; the concentration is either increased if the previous subject did not respond or decreased if they did. The MAC is usually calculated either as the mean concentration of equal numbers of responses and no-responses or is the mean concentration of pairs of "response–no response".

Logistic Regression Model

When the pharmacological effect is difficult to grade, then it may be useful to estimate the probability of achieving the effect as a function of plasma concentration. Effect measures such as

movement/no movement or rousable/non-rousable are dichotomous. Logistic regression is commonly used to analyse such data and the interpolated EC_{50} value refers to the probability of response. For example, an EC_{50} of 0.52 mg/L for arousal after ketamine sedation in children has been estimated using this technique [104].

Linking PK with PD

A simple situation in which drug effect is directly related to concentration does not mean that drug effects parallel the time course of concentration. This occurs only when the concentration is low in relation to EC_{50}. In this situation the half-life of the drug may correlate closely with the half-life of drug effect. Observed effects may not be directly related to serum concentration. Many drugs have a short half-life but a long duration of effect. This may be attributable to induced physiological changes (e.g. aspirin and platelet function) or may be due to the shape of the E_{max} model. If the initial concentration is very high in relation to the EC_{50}, then drug concentrations 5 half-lives later, when we might expect minimal concentration, may still exert a considerable effect. There may be a delay due to transfer of the drug to effect site (NMBD), a lag time (diuretics), physiological response (antipyresis), active metabolite (propacetamol) or synthesis of physiological substances (warfarin).

A plasma concentration–effect plot can form a hysteresis loop because of this delay in effect. Hull et al. [124] and Sheiner et al. [125] introduced the effect compartment concept for muscle relaxants. The effect compartment concentration is not the same as the blood or serum concentration and is not a real measurable concentration. It has a negligible volume and contains negligible blood. A single first-order parameter ($T_{1/2keo}$) describes the equilibration half-time. This mathematical trick assumes concentration in the central compartment is the same as that in the effect compartment at equilibration, but that a time delay exists before drug reaches the effect compartment. The concentration in the effect compartment is used to describe the concentration–effect relationship [126].

Adult $T_{1/2keo}$ values are well described, e.g. morphine 16 min, fentanyl 5 min, alfentanil 1 min, propofol 3 min. This $T_{1/2keo}$ parameter is commonly incorporated into TCI pumps to achieve a rapid effect site concentration. The adult midazolam $T_{1/2keo}$ of 5 min [127] may be prolonged in the elderly, resulting in overdose if this is not recognised during dose titration.

The $T_{1/2keo}$ for propofol in children has not been described. We might expect a shorter $T_{1/2keo}$ with decreasing age based on size models [128], and this is exactly what has been described by Jeleazcov et al. [129]. Similar results have been demonstrated for sevoflurane and BIS [130]. If unrecognised, this will result in excessive dose in a young child if the effect site is targeted and peak effect (T_{peak}) is anticipated to be later than it actually is because it was determined in a teenager or adult. Unfortunately, integrated PK-PD studies in children are lacking. Available paediatric propofol $T_{1/2keo}$ values have been determined by the application of published PK data to PD observations only [131, 132].

Adverse Effects

Neonates and young children may suffer permanent effects resulting from a stimulus applied at a sensitive point in development. For example, congenital hypothyroidism, if untreated causes lifelong phenotypic changes. The incidence of vaginal carcinoma is high in children of mothers treated with stilboesterol during pregnancy [133]. There are concerns that neonatal exposure to some anaesthetic agents (e.g. ketamine, midazolam) may cause widespread neuronal apoptosis and long-term memory deficits [134, 135].

Anaesthesia, analgesia or sedation, generally involves examination of immediate adverse effects such as PONV, hypotension or respiratory depression. A dose–response curve for intravenous morphine and vomiting was investigated in children having day-stay tonsillectomy. Doses above 0.1 mg/kg were associated with a greater than 50% incidence of vomiting [136]. These data are similar to those in children undergoing inguinal herniorrhaphy [137]; suggesting that

lower doses of morphine are associated with a decreased incidence of emesis after day stay surgery, and encourage the use of alternative analgesic drugs.

Drug Interactions

Drug interactions can increase or decrease response mediated through either PK or PD routes. Phenobarbitone induces glucuronide conjugation maturation in neonates. An increase in the $T_{1/2keo}$ of d-tubocurarine with increasing inspired halothane concentrations has been demonstrated [138]. Halothane is a negative inotrope [139] and reduces skeletal muscle blood flow [140], so it seems reasonable to interpret changes in $T_{1/2keo}$ as due to changes in blood flow. Inhalation anaesthetic agents can also prolong duration of block and this effect is agent specific. Sevoflurane potentiated vecuronium more than halothane; when compared to balanced anaesthesia, the dose requirements of vecuronium were reduced by approximately 60 and 40%, respectively [141].

Anaesthetic drug interactions traditionally have been characterised using isobolographic analysis or multiple logistic regression. Minto et al. [142] has proposed a model based on response-surface methodology. Computer simulations based on interactions at the effect site predicted that the maximally synergistic three-drug combination (midazolam, propofol and alfentanil) tripled the duration of effect compared with propofol alone. Response surfaces can describe anaesthetic interactions, even those between agonists, partial agonists, competitive antagonists and inverse agonists [142].

Synergism between propofol and alfentanyl has been demonstrated using response-surface methodology. Remifentanil alone had no appreciable effect on response to shaking and shouting or response to laryngoscopy while propofol could ablate both responses. Modest remifentanil concentrations dramatically reduced the concentrations of propofol required to ablate both responses [143]. When comparing the different combinations of midazolam, propofol and alfentanil, the responses varied markedly at each end point assessed and could not be predicted from the responses of the individual agents [144]. Similar response-surface methodology has been taken for investigation of the combined administration of sevoflurane and alfentanil [145] and remifentanil and propofol [146] on ventilation control. These combinations have a strikingly synergistic effect on respiration, resulting in severe respiratory depression in adults. These synergistic associations can be extended to paediatric sedation techniques. It is little wonder that the use of three or more sedating medications compared with 1 or 2 medications was strongly associated with adverse outcomes [147].

Defining Target Concentration

An effect site target concentration has been estimated for many drugs used in anaesthesia, analgesia and sedation. For example, a propofol target concentration of 3 mg/L in a typical patient can be achieved using pre-programmed TCI devices. A BIS monitor can then be used to manually adjust infusion rate to achieve a desired target effect in the specific individual. The luxury of such a feedback system is not available for most drugs.

A target concentration of 10 μg/L is used for morphine analgesia. Observations in children after cardiac surgery suggested that steady-state serum concentrations greater than 20 mg/L resulted in hypercarbia ($PaCO_2 > 55$ mmHg) and depressed CO_2 response curve slopes. During wash-out, morphine concentrations more than 15 μg/L resulted in hypercarbia in 46%, whereas concentrations less than 15 μg/L were associated with hypercarbia in 13% of children. No age-related differences in respiratory effect were seen in these studies at the same serum morphine concentration [36]. Observation or self-reporting pain scales are used as part of the feedback loop for dose incremental changes.

The target concentration may vary, depending on the desired target effect. The target concentration for ketamine analgesia (0.25 mg/L) is quite different from that of anaesthesia (2 mg/L) [148].

Conclusions

Children can be considered as small adults; size factors alone can explain many differences between children and adults. Neonates are developing children; maturation processes over the first few years of life have dramatic impact on both PK and PD. Size, age and OF models can be used to characterise PK changes in the paediatric population. Although PD differences between neonates and children are recognised, there is little information describing maturation of these PD differences. Achievement of a target effect with minimal adverse effect is the key to anaesthetic, analgesic and sedation drug use. Pharmacodynamic models are useful tools to identify a target effect and concentration at which that occurs. Pharmacokinetic models, in turn, point to dose that will achieve that target concentration. The population approach to modelling has proven beneficial to exploring PKPD differences in children. The impact of other drugs, active metabolites, stereoisomer interactions and PGs on the concentration–response relationship remains undefined for many drugs.

An understanding of PK and PD of drugs commonly used in children of all ages is vital for sensible sedation regimens. Simple infusion regimes for morphine, targeting a plasma concentration of 10 μg/L, that vary with age have been proposed [59]. Ketamine regimens that target an effect (e.g. arouses slowly to consciousness with sustained painful stimulus) are reported [149]. TCI pumps are dependent on an accurate knowledge of PK and PD parameters. Currently, this technique is unavailable for even propofol and remifentanil in infants under 2 years of age because such information is lacking. Once this information is available, it will be possible to programme these TCI pumps to deliver any adequately investigated drug to any specific target concentration in either plasma or effect site [150]. However, even with a good knowledge of PK and PD parameters estimates, there remains considerable between-patient variability of both PK and PD parameters. This variability can result is some patients not achieving the desired sedation level because they are “too light” or “too deep.” Concentration monitoring (e.g. propofol in expired breath) may reduce target concentration scatter attributable to PK parameter variability. Infusions can be increased or decreased to achieve the desired target. Unfortunately, the concentration–response curve is also associated with considerable variability, and target effect monitoring (e.g. modified EEG signalling) can be used to further modulate drug delivery for the individual. Modified EEG signalling and feedback loops that automatically regulate infusion rates to achieve desired effect are already available in adult practice and widely used for propofol. Children should not be denied similar levels of sophistication. This level of sophistication will only come once we have elucidated and understood paediatric PK and PD and the factors that contribute to their variability (e.g. age, size, PGs).

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Billing and Reimbursement for Sedation Services

10

Devona J. Slater

Sedation is intended to provide safe and effective administration of drugs to relieve anxiety and reduce pain. The aim of any sedation service is to maximize patient comfort, while monitoring the patient continuously, so that the procedure can be completed in a safe environment. The billing for sedation services has to be representative of the actual services that the physician delivers. When pediatric sedation services are hospital based (the sedation providers are employed by the hospital), the activity of the hospital-employed cannot be included in the professional charges: only the actual services that the physician alone performs can be utilized in billing for his/her professional service. Professional services should be billed by the entity that employs the physician. No matter whether the physician is in private practice or is employed by a large entity, the billing rules for professional services apply.

In December of 2009, the Revised Hospital Anesthesia Services Interpretive Guidelines outlined that all services involving anesthesia must be organized under a single anesthesia department. The memorandum specifically states that all services along the continuum of anesthesia services must be organized under this Anesthesia Service, directed by a qualified physician and consistently implemented in every hospital department and setting that provides any type of anesthesia services [1]. This will require sedation departments to work closely with the hospital based anesthesia department to credential providers and assess airway management skills.

The guidelines also specifically address qualified providers for deep sedation and the requirements for pre and post operative visits. To bill for anesthesia services, the provider must fulfill the requisite documentation: the guidelines are specific in what is expected for preanesthesia and post anesthesia evaluations to determine if the services can be considered as general, regional, deep sedation or Monitored Anesthesia Care (MAC). Any of these services restrict the providers to only allow for a "qualified" anesthesia provider to perform the pre-anesthesia evaluation within a 48 hour window. They clearly define qualified anesthesia providers as an anesthesiologist, a Certified Registered Nurse Anesthetist (CRNA) or an anesthesia assistant (AA) within scope of practice. Their interpretation extends the qualified providers to physicians who have been credentialed to deliver sedation services (anesthesia service privileges).

These guidelines directly impact the way anesthesia departments will be judged when the Centers for Medicare and Medicaid Services (CMS) conduct a site visit. While these auditors are looking for elements in which to judge the

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hospital to determine whether it will be allowed to continue participation in the Medicare program, Hospitals will look to physicians to ensure that documentation meets the expectations. While the interpretative guidelines are not physician payment rules, hospitals could not survive if they were excluded from government programs. Physicians do have a duty to ensure that the services they deliver meet with the guidelines expected for hospital participation [1].

An item of importance in the Interpretative Guidelines is the definition of "immediately available." This phrase has often been the center of different interpretation and some consternation. The transmittal states that the CRNA/AA must be supervised by a physician who is physically located within the same area. Although this definition is a bit restrictive as it is still vague, the intention and expectations of the government are clear. The government is expecting an area to be defined as the same "labor and delivery unit," contained within a procedural area, such as radiology, Gastroenterology (GI) or Cardiac Catheterization Suite. In the strict definition, the guidelines would require a qualified anesthesiologist to be in each area. While no specific mention was singled out for sedation services, one could conclude that the physician overseeing the sedation services would need to remain present in the same area that the deep sedation services are delivered to fulfill the guideline [1].

The CMS guidelines were revised February 5, 2010 and titled: Revised Hospital Anesthesia Services Interpretive Guidelines – State Operations Manual (SOM) Appendix A [2]. The guidelines presented a proposed organization plan for Hospital Anesthesia Services [2] (Fig. 10.1). Important amendments included the recognition of deep sedation as a service which falls under MAC. Moderate sedation, in contrast, did not fall under the requirement for anesthesia administration and supervision. MAC according to these guidelines could only be administered by:

1. A qualified anesthesiologist
2. An MD or DO (other than an anesthesiologist)
3. A dentist, oral surgeon or podiatrist who is qualified to administer anesthesia under State law
4. A CRNA who is supervised by the operating practitioner or by an anesthesiologist who is immediately available if needed; or

   A CRNA is defined in §410.69(b) as a "…registered nurse who: (1) is licensed as a registered professional nurse by the State in which the nurse practices; (2) meets any licensure requirements the State imposes with respect to non-physician anesthetists; (3) has graduated from a nurse anesthesia educational program that meets the standards of the Council on Accreditation of Nurse Anesthesia Programs, or such other accreditation organization as may be designated by the Secretary; and (4) meets the following criteria: (i) has passed a certification examination of the Council on Certification of Nurse Anesthetists, the Council on Recertification of Nurse Anesthetists, or any other certification organization that may be designated by the Secretary; or (ii) is a graduate of a program described in paragraph (3) of this definition and within 24 months after that graduation meets the requirements of paragraph (4)(i) of this definition" [2].

5. An anesthesiologist's assistant under the supervision of an anesthesiologist who is immediately available if needed

   An anesthesiologist's assistant is defined in §410.69(b) as a "…person who – (1) works under the direction of an anesthesiologist; (2) is in compliance with all applicable requirements of State law, including any licensure requirements the State imposes on nonphysician anesthetists; and (3) is a graduate of a medical school-based anesthesiologist's assistant education program that – (A) is accredited by the Committee on Allied Health Education and Accreditation; and (B) includes approximately two years of specialized basic science and clinical education in anesthesia at a level that builds on a premedical undergraduate science background" [2].

These CMS guidelines were again revised in January 2011 in the PUB 100-07 State Operations Provider Certification which revises Appendix A for various provisions of 42 CFR 482-52 concerning anesthesia services [3]. These revisions were made in response to feedback from practitioners. Important changes in these guidelines stem from the CMS acknowledgement that the individual hospitals may establish their own policies and procedures with respect to the qualifications of analgesia providers and the clinical situations which distinguish anesthesia from analgesia. The policies must follow nationally

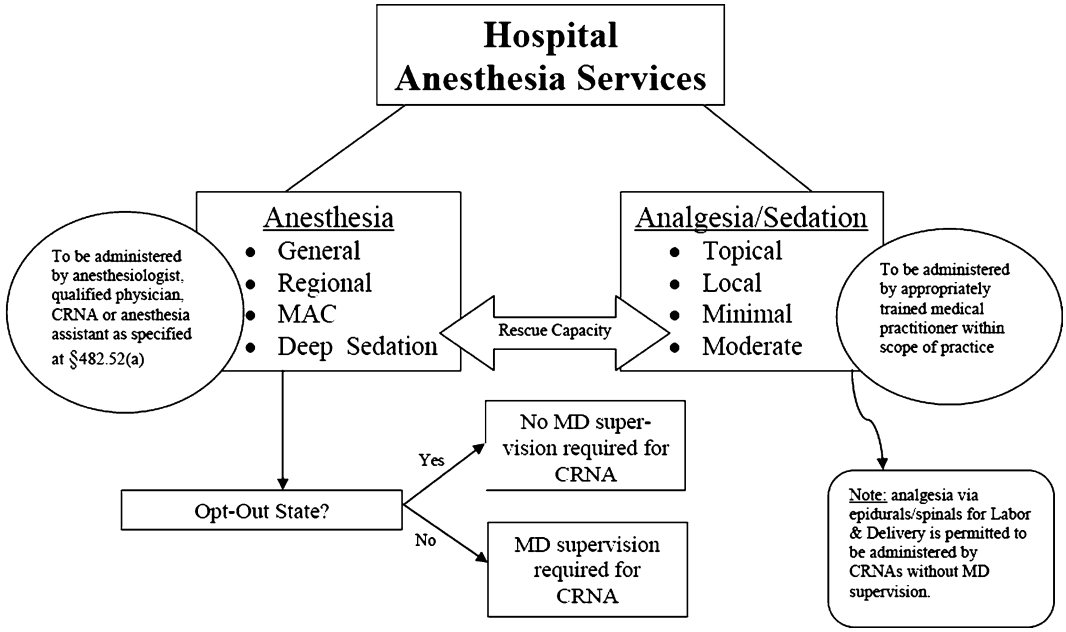

Fig. 10.1 Proposed organization plan for Hospital Anesthesia Services (reprinted with permission from Revised Hospital Anesthesia Services Interpretive Guidelines – State Operations Manual (SOM) Appendix A) [2]

recognized guidelines and can include guidelines of one or more specialty societies.

While these guidelines specifically address the hospital's participation in Medicare and Medicaid services, they have not been applied to Part B reimbursement methodology, the physician component of payment for Medicare services. History tells us that once applied to the hospital side of reimbursement, it is only a matter of time before these regulations make their way to physician payment rules. Physicians should expect that these guidelines may be applied to Medicare Part B reimbursement language for professional services in the future.

The American Medical Association (AMA) allows any physician to use any code in the CPT-4 book. The CPT-4 reference book is the *Current Procedural Terminology* (*CPT*®), Fourth Edition [4]. It is published annually by the AMA and is a set of codes, descriptions, and guidelines intended to describe procedures and services performed by physicians and other health care providers. Each procedure or service is identified with a five-digit code. The use of CPT codes is recognized industry wide and simplifies the reporting of services. As stated above, any physician may use any code as long as the services that are delivered are reported accurately. Documentation is critical to justify the reason for the service as well as the procedure performed. Many insurance companies have policies specifically addressing the use of anesthesia codes by nonanesthesiologists. Most will reimburse MAC services delivered by non-anesthesiologists, provided that the physician bills the appropriate anesthesia code (00100-01999). Using these anesthesia codes, however, requires that the physician

- Performs pre-evaluation and post evaluation services
- Documents the anesthesia time in minutes
- Normally reimburses these services regardless of place of service
- Meets the requirements for MAC

The service documentation for MAC or deep sedation services must mirror that of a general or regional anesthetic in order to be billed with the anesthesia codes. It is recommended that if billing anesthesia codes, physicians should document in the anesthesia record format. This would

include constant monitoring and the notation of drugs delivered on a time sensitive record.

In order to understand how best to bill for sedation services; it is important to first evaluate the services which are being provided for the patient. The documentation as well as the actual services rendered will direct how the service can be coded and billed. Sedation services are coded differently based on the depth of sedation given. This assessment is a medical decision made by a provider and cannot (and should not) be determined by a medical coder. The provider must document whether minimal, moderate, deep sedation or a general anesthetic is being delivered.

Minimal Sedation

Minimal sedation is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected. If providing minimal sedation services there is no additional payment allowed. There are no codes to represent the service of minimal sedation. Minimal sedation is normally bundled into the payment for a procedure.

Moderate Sedation

Moderate sedation is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain the patient's airway and spontaneous ventilation is adequate. It is important that moderate sedation does not include minimal sedation (anxiolysis), deep sedation or MAC.

Moderate sedation codes were introduced by the American Medical Association (AMA) in 2006 to recognize services that are in between minimal sedations and that of deep sedation (MAC). The services include (a) a patient assessment, (b) establishment of IV access, (c) administrations of agents, (d) sedation maintenance, (e) monitoring of oxygen saturation, heart rate, and blood pressure, and (f) recovery of the patient. The AMA chose to keep with the logic of anesthesia billing, allowing the coding to be billed by time. The codes require the documentation of "intra-service" time. Intra-service time is defined to start with the delivery of the sedation agent and ends when the procedure is finished.

The coding of moderate sedation services are reported by CPT codes 99143 through 99150 [4] (Fig. 10.2). The actual coding is specific to the practitioner delivering the service, the age of the patient, the facility, and the amount of intra-service time. The physician performing the procedure may also supervise, regardless of the location. In this situation there must be an independent trained third party person to monitor the patient. In contrast, CPT codes 99148 through 99150 are services provided by a second physician and are only allowed in a facility setting such as the hospital. The codes are specific to patients under or over the age of five and require it to be physician administered and the physician must stay with the patient the entire time. Figure 10.2 outlines each of these codes [4].

Currently the Medicare system, and many commercial carriers, allow additional payment for moderate sedation as long as it is not for a code that includes sedation services in the descriptor; see CPT-4 Book current year, Appendix G. At the time of this writing, the moderate sedation codes have been assigned a status indicator of "C" under the Medicare Physician Fee Schedule. The "C" designates that these services are carrier priced, meaning that each individual Medicare intermediary determines the amount of payment appropriate for the service. At this time, CMS has not established relative value units for these services and payments vary based on the carrier and the region of the country. For commercial payors, rates range from $40 to $200 per unit depending on the geographical area of the country and the specific carrier.

The confusion in billing for sedation services occurs when a separate physician delivers only a part of the sedation services, such as the triage, evaluation and sedation plan followed by his

⦸99143 Moderate sedation servicea [other than those services described by codes 00100-01999) provided by the same physician performing the diagnistic or therapeutic service that the sedation supports, requiring the presence of an independant trained observer to assist in the monitoring of the patient's level of consciousness and physiological status: younger than 5 years of age, first 30 minutes intra-service time

DPT Assistant Feb 06.9. May 06:19.20 Feb 08.5. Nov 09. 11. Dec 09:10: *CFT Changes An Insider's View 2006*

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⦸99144 age 5 years or older, first 30 minutes intra-service time

DPT Assistant Feb 06.9. May 06:19.20 Feb 08.5. Nov 09. 11. Dec 09:10: *CFT Changes An Insider's View 2006*

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◆99145 each additional 15 minutes intra-service time (List seperately in addition to code for primary servce

DPT Assistant Feb 06.9. May 06:19.20 Feb 08.5. Nov 09. 11. Dec 09:10: *CFT Changes An Insider's View 2006*

Clinical Examples in Radiology Winter 06.18. Summer 06: 1-3. Fall 07:12. Spring 08:1,2, Summer 08: 1, 2

[Use 99145 in conjunction with 99143, 99144)

99148 Moderate sedation services [other than those services described by codes 00100-01999) provided by a physician other than the health care professional performing the diagnostic or therapeutic service that the sedation supports, younger than 5 years of age, first 30 minutes intra-service time

DPT Assistant Feb 06.9. May 06:19.20 Feb 08.5. Nov 09. 11. Dec 09:10: *CFT Changes An Insider's View 2006*

Clincal Examples in Radiology Winter 06:18

99149 Age 5 years or older, first 30 minutes intra-service time

DPT Assistant Feb 06.9. May 06:19.20 Feb 08.5. Nov 09. 11. Dec 09:10: *CFT Changes An Insider's View 2006-2008*

Clincal Examples in Radiology Winter 06:18

99150 each additional 15 minutes intra-service time (Lise seperately in addition to code for primary service)

DPT Assistant Feb 06.9. May 06:19.20 Feb 08.5. Nov 09. 11. Dec 09:10: *CFT Changes An Insider's View 2006*

Clincal Examples in Radiology Winter 06:18

(Use 99150 in conjunction with 99148, 99141

Fig. 10.2 Coding of moderate sedation services (from Current procedural terminology [4])

supervision of a sedation nurse. There is no coding reference for this type of activity. However, it is the author's opinion that billable services would most closely represent an Evaluation and Management code for the medical decision making service of clearing the patient for the anesthetic and providing a plan of care. These codes would most likely fall into the new patient or established patient codes in either the inpatient or outpatient setting. It would be inappropriate to bill the moderate sedation codes or anesthesia codes if the physician was a nonanesthesiologist and the actual sedation was not delivered by the physician.

Billing for Evaluation and Management services are classified into facility categories, most frequently these will be the outpatient (office) visits or hospital visits. Within each class there are usually sub categories of new or established patients. Physicians must remember that they are being paid for the medical decision they are making and the work involved in making that decision. Over-documenting areas of the history of present illness, review of systems and examination to drive up the level of evaluation and management coding is inappropriate.

While there are many tools and documents written about coding of evaluation and management services, this chapter will only address the elements of evaluation and management coding that are of particular importance for sedation providers. It is not intended to be a complete coding tool for evaluation and management coding.

The two main components which determine and substantiate the coding and billing for sedation services are the medical necessity and the actual medical decision process. The degree of documentation should support the level of service billed. The code should be selected based on the content of the service. Although the chief complaint or presenting problem may be obvious, it is still recommended to include a brief medical necessity statement with the documentation to support the need for sedation service: For example, it is understood that in young children, sedation services are necessary to perform procedures. Careful documentation is critical in the event that at a later period (maybe even years later) the reviewer disagrees with the necessity of having a separate physician provide the sedation service. Carriers may take up to 7 years to contest or disagree with a charge. If government agents believe fraud was involved, they may go back indefinitely. Therefore, a well documented record to explain the thought process of why sedation is warranted is the best protection against health care scrutiny.

Key Components of Evaluation and Management Services Documentation

All evaluation and management services have specific components. There are seven components that assist coders in translating the documented work into the appropriate code selected. Only three are required (key) components that must be documented for all visits. These three key components are: (1) patient history, (2) physical examination, and (3) medical decision making.

The first specific key component is the *patient history*. The history section contains several elements:

1. The chief complaint/presenting problem
2. The history of present illness
3. A review of systems
4. The past medical, family and social history of the patient

This history section should include the justification and rationale for requiring a separate physician to provide the sedation services.

The second of the key components is the *physical examination*. The examination documentation must contain up to date information regarding the patient's condition at the time of the exam and should describe the results and findings of body areas or organ systems that are actually examined by the physician during the encounter. It is specifically noted that this type of physical examination should be based on the physician's clinical judgment and directed toward that which is medically indicated to support the medical decision.

The final of the three key components is the *medical decision.* The medical decision is commonly referred to as "the thought process of the physician." It should be a statement or statements that represent the complexity of the decision-making process involved in selecting a plan for the management and delivery of sedation services. This assessment should include the critical elements which were considered in deriving the sedation plan as well as the intended depth of sedation required. There is not a clearly defined level of risk involved in providing sedation. The CMS guidelines define the degree of risk as low to moderate, depending on the nature of the presenting problem(s) of the patient and the procedure.

If the evaluation and management plan of the sedation is performed by a provider separate from that who will be delivering and monitoring the sedation, it would be appropriate to charge for the initial services under evaluation and management codes. These concurrent care services are payable when the physician plays an active role in the patient's treatment or the treatment plan. The medical diagnosis should reflect the need for medical evaluation and management as a necessity for the delivery of subsequent sedation services.

Deep Sedation

Deep Sedation is defined as a drug-induced depression of consciousness during which patients cannot be easily aroused following repeated or painful stimulation. The ability to independently maintain ventilatory function during this time may be impaired and assistance may be required to maintain the airway.

One cannot discuss deep sedation and MAC without understanding the differences. MAC can be light, moderate or deep sedation delivered by a provider who is prepared and qualified to convert to general anesthesia.

Insurance companies are interested in addressing the rules surrounding medical necessity for the separate anesthesia provider as this adds to the cost of the service. The American Society of Anesthesiologists (ASA) position statement defines medically necessary services as those which alleviate emotional or psychological duress or pain while undergoing a surgical, obstetrical or other therapeutic/diagnostic procedure. The ASA supports that the level of sedation should be based on the medical judgment of a physician who is trained in anesthesia, in conjunction with the physician performing the procedure. The targeted level of sedation must consider all aspects of the patient's health as well as the procedure to be

performed. Many insurance companies do not recognize this broad definition and relate the medical necessity to the ASA status of the patient. To support the need for separate anesthesia providers, additional diagnosis, ICD-9 codes, must accompany the justification for the procedure and sedation. The ASA status is the assignment of a P code to assess the degree of a patient's "sickness" or "physical state" prior to selecting the sedatives or prior to performing the procedure. It helps determine the "risk" that a patient presents. Some insurance companies designate an ASA status of P3 or greater to justify the need for a separate anesthesia provider.

In billing an anesthesia code from the CPT-4 book, non-anesthesia physician providers are held to the same requirements of documentation as that which is required from an anesthesia provider. This includes:

1. A preoperative assessment that would review abnormalities of the major organ systems
2. An airway assessment
3. A history of any previous experience with sedation or anesthetics
4. A review of drug allergies and current medications
5. A review of tobacco, alcohol or substance abuse
6. The time and nature of last oral intake
7. Assignment of the ASA physical status

During the actual medical procedure the appropriate monitoring must be performed and would include:

1. Heart rates
2. Oxygenation
3. Respiratory frequency and adequacy of pulmonary ventilation
4. Blood pressure and cardiac monitoring

Vital signs should be documented at 5 min intervals.

A post anesthesia assessment recording physiological status, mental status and a pain level should be recorded prior to transferring care to post anesthesia care unit personnel. The medical record should document that the patient was discharged from the recovery area only after meeting clinical criteria.

General, Regional and Monitored Anesthesia Care

Billing done for anesthesia services allows the assignment of base units added to time units, usually assigned in 15 min increments, and then adjusts for modifying circumstances or physical status units. The ASA base units are assigned to every surgical CPT code and reflect the difficulty of the anesthesia services, including the usual preoperative and postoperative care. The CPT procedure code is cross-walked to the appropriate anesthesia code based on region of the body, technique and the age of the patient. Unlike with other specialties, anesthesia can only bill for a single procedure, even when multiple procedures are performed at the same setting. In these circumstances, the anesthesia may be billed for the procedure with the highest unit value. After the selection of base units has been established, anesthesia time is calculated and added to the base units. Anesthesia time is defined to start when the provider begins to prepare the patient for anesthesia care and ends when the patient is safely placed in the care of the post anesthesia care unit. The total number of minutes is then divided by a number that is customary in the local area, usually 15 min. This will convert the minutes into units that are then added to the base unit value. Qualifying circumstances and physical status modifiers carry a base unit value in certain circumstances. Patients with severe systemic disease or cases that meet the definition of qualifying circumstances may be allowed to add extra units. It is best to consult the ASA Current Year Relative Value Guide to establish billing for units.

In some circumstances, the insurance carrier may require "modifiers" to define "who provided the service" and other special modifiers, when the services were MAC. The first modifiers appended to the anesthesia service are termed as medical direction modifiers. *Only anesthesiologists are allowed to direct qualified anesthesia personnel and provide multiple services at one time*. The AA modifier designates that the physician alone provided the service. The QK

modifier would represent medical direction services of a CRNA, AA, anesthesia resident/trainee or Student Registered Nurse Anesthetist (SRNA) and if appropriate would have a matching claim from those providers with the QX modifier.

When providing MAC the second set of modifiers appended on the claim form should identify the MAC service with one of the following informational modifiers:

QS – Designates MAC

G8 – Designates the MAC services are necessary because the procedure is noted as deep, complex, complicated or markedly invasive

G9 – Designates the MAC services are necessary because the patient has a personal history of cardiopulmonary disease

The final modifiers that may be appended would be the physical status modifiers denoting the condition of the patient. These are outlined in the CPT-4 instructions and all start with P.

Fee for Services

Payment for anesthesia services is determined on a unit basis. Payment is not restricted to specialty designation as long as the services are equal in nature. Unit values vary from a low of a few dollars (usually those paid by state or government programs) to over $100.00 per unit.

Contracting with commercial payors for anesthesia services is a key element for success in a sedation program. Meeting with payors to explain the nature of the service and the allowance of nonanesthesia personnel to be paid under anesthesia codes are large hurdles for any sedation program. "Major" insurance carriers should be identified and then addressed individually. To justify reimbursement, providers need to keep in mind the qualifications of the provider, the medical necessity of the service and the cost benefit to the insurance company. Negotiations will require that the nonanesthesiologists demonstrate that they can provide the same level of care as the local anesthesiologists and that the care is medically necessary for the safety of the patient. The important thing for providers to remember is that quality of care is always assumed by insurance executives.

Payment for moderate sedation codes as well as evaluation and management codes are based on a flat fee service. These reimbursement amounts vary greatly by payor. Most carriers will base reimbursement as a percentage of the Medicare Resource Based Relative Value System (RBRVS) reimbursement system. Management personnel should carefully evaluate reimbursement and negotiate rates with payors in order to reflect a fair and appropriate payment for the intensity and time required for the sedation services rendered.

Legal Consequences of Incorrect Coding/Documentation

If one is to choose billing for these services as a non-anesthesiologist, it is important to be compliant with documentation of billing for anesthesia time and concurrency. As defined, anesthesia time is face to face contact time with the patient. This is a concept that the enforcement agencies have paid particular attention to and will continue to do so. Using circulating nursing records, operative reports and postanesthesia care unit records, auditors are able to verify if time reported is accurate. Concurrency again can only be reported by an anesthesiologist and even then close attention must be paid to exactly what services were being delivered at any one time. The government does not allow you to medically direct and personally perform services at any one given time. Knowing and understanding that an anesthesiologist cannot medically direct and personally perform services at the same time is key to staying out of compliance trouble. Deep sedation services will have the same constraints remembering that one physician can only attend to one patient at a time.

No matter what specialty, the government's activities to recoup monies that have been paid inappropriately will continue. The realization is that the government has a tremendous return on fraud and abuse investment dollars and will continue to scrutinize services. Physicians can be penalized monetarily or in some cases where fraud is involved, jail time, a loss of medical licensure or exclusion from the Medicare and

Medicaid programs. It is for this reason that it is critical to implement compliance programs.

The implementation of a compliance program can be a challenge, as many physicians are still unclear as to "What makes an effective compliance program?" The most effective programs will have integrated the compliance into the day-to-day operations of the group and will incorporate the seven federal sentencing guidelines into simple day to day procedures.

The first of the sentencing guidelines require written policies and procedures. The policies and procedures that have been written for the program need to be understood by all members of the group. It is important that employees have guidance in understanding the basic concepts discussed in the plan. Plan policies could be tested and results kept in personnel files to assure that everyone knows the commitment of the group to the compliance plan and the intention to only bill for services that are appropriately documented.

The sentencing guidelines specifically ask that a compliance officer be designated for the group. The group must evaluate the performance of the compliance officer and while the compliance officer does not necessarily have to be a physician, he has the absolute authority to hire and fire personnel. The Board should assess whether the compliance officer has sufficient knowledge and education to deal with the assigned responsibilities. It would be important for them to judge whether appropriate auditing and education is being carried out to fulfill the requirements of compliance. Compliance committee minutes and processes of handling any reported violations should be reviewed to ensure all issues have been dealt with and recorded as to corrective action.

Education and training of all levels of employees must be done according to the sentencing guidelines. Courses and educational materials should reflect the important aspects of the group's compliance program. Ongoing training and demonstration of evaluation of knowledge should be recorded. Accurate records of content, frequency and attendees are very important in order to demonstrate educational efforts.

The sentencing guidelines stress open communication and it is considered an essential element in a compliance program. In today's environment, a provider cannot possibly have an effective compliance program if it receives minimal or no feedback from employees. Simply recording that there have not been any violations reported is not enough. A record of questions regarding policies, and any guidance given or research done by the compliance officer or committee should be documented to show open lines of communication.

One of the key components of the sentencing guidelines stresses ongoing monitoring and auditing. Auditing, both internal and external is critical to a successful compliance program. Frequency and the extent of the audit function will vary depending on the size and issues identified by the group. Audits must not discriminate between providers and must address issues that are considered "hot spots" in the specialty. Audits should ensure that elements set forth in the compliance plan are being monitored and that auditing techniques are valid and conducted by objective reviewers. For example, we know sedation programs may be using Evaluation and Management coding to bill for services. A compliance professional would want to audit these services to see if they meet the criteria for billing. If deep sedation programs are billing with anesthesia codes, an audit regarding anesthesia time, modifiers and documentation of the components of an anesthesia service should be reviewed.

The sixth requirement of the federal sentencing guidelines requires suspected violations to be thoroughly investigated. When a provider learns of an issue it is important to contact legal counsel to properly handle and circumvent any exposure to the group. If evidence exists that misconduct has occurred, counsel will be needed to work through the process of self-disclosure.

Finally, disciplinary action constitutes the last key ingredient to the federal sentencing guidelines. Disciplinary action must be taken on those employees who fail to adhere to the group's standards set forth in the compliance program. Discipline must be applied consistently between employees regardless of the employee's level in the corporation and documented. Senior management must demonstrate a serious commitment to foster a climate that will require adherence to all federal and state regulations.

In summary, compliance must be an activity that is incorporated into the day-to-day practices of the group. Government investigations will continue. All new healthcare legislation mentions the need for continued efforts to fight fraud and abuse. The best protection for a group is an active compliance program.

Summary

There is no single way to bill "sedation" services. Anesthesia/sedation services must begin with careful documentation to adequately reflect the role of the sedation care provider throughout the entire sedation process. Careful consideration should be used to determine the appropriate coding methodology. In many instances the coding should be determined on a case-by-case basis after careful review of the documentation and nature of physician services. It is recommended to regularly have an independent review of documentation, coding and billing in order to avoid inadvertent mistakes that may be audited by authorities. A coding professional can assist in helping ascertain accurate coding but also determine the best way to achieve best reimbursement for service.

Case Studies

Below are scenarios of how cases may need to be billed based on the personnel involved, the level of sedation delivered and the intensity of the service. These are hypothetical examples and in no way reflect medical care.

A pediatric radiologist in the outpatient hospital setting would like to have sedation services for the patient's MRI.

1. If the radiologist supervises a Registered Nurse (RN) giving the moderate sedation, you would review codes 99143 through 99145.
2. If the radiologist requests another physician, such as a hospitalist, to perform the moderate sedation, you would review codes 99148 through 99150.
3. If the radiologist uses the hospital sedation service, which is headed by the hospitalist who: sees the patient, clears the patient for the moderate sedation services and then supervises a special trained RN to administer the moderate sedation the physician may only bill for an evaluation and management service based on elements evaluation and management elements documented and the medical decision making performed.
4. If the radiologist requests that deep sedation be given and someone who has the credentials to deliver deep sedation provides the service, you should review the ASA code 01922 and review the anesthesia record for the appropriate time billing.
5. If a nonanesthesiologist or anesthesiologist is able to provide MAC for the radiologists, you should review ASA code 01922 and append the QS modifier designating that it is MAC and review the anesthesia record for the appropriate time billing.

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Part II

Sedation Models Delivered by Different Specialties: A Global Voyage

11 The Pediatric Hospital Medicine Sedation Service: Models, Protocols, and Challenges

Douglas W. Carlson

The field of pediatric hospital medicine has grown rapidly over the past decade. The term "hospitalist" was initially defined in an article in the New England Journal of Medicine in 1996; it is defined as spending half or more of one's work in the area of inpatient care. There are pediatric hospitalists on the medical staffs of most children's hospitals in USA, as well as on the medical staffs of an ever-increasing number of community hospitals.

Since pediatric hospitalists spend a majority of their time caring for hospitalized patients, they are in a position to fully understand the clinical needs of those patients. Pediatric hospitalists identify the needs of patients and work within systems to provide appropriate care. They also work to provide care safely and effectively.

Care of hospitalized patients often requires diagnostic and therapeutic procedures. Often, many of these procedures are best done using sedation and analgesia. It is the responsibility of the pediatric hospitalist to either perform or arrange for these procedures. It is also the responsibility of the pediatric hospitalist to guarantee that any sedation or analgesia needed to perform these procedures is delivered in the safest and most effective way possible. Pediatric hospitalists can ensure safe sedation of patients by working within their systems and asking appropriately trained staff to perform sedations, or by obtaining the necessary skills to perform the sedations themselves.

In a survey conducted by the Pediatric Research in Inpatient Settings Network (PRIS), 54% of pediatric hospitalists reported providing moderate and/or deep sedation. There was no significant difference between sedation providers and nonproviders in terms of gender, geographic location, type of residency training, residency size, or involvement in teaching. Pediatric hospitalist sedation providers are more likely to work in a community hospital, to work in a nonacademic environment, and to have been a pediatric hospitalist for over 6 years. Sedation providers are also significantly more likely to be the physician of record in the PICU, to spend over 75% of their professional time as a pediatric hospitalist, and to not participate in research [1].

Sedation drugs reported by those pediatric hospitalists providing sedation:

94% Opioid/benzodiazepine combination
70% Chloral hydrate
51% Ketamine
46% Pentobarbital
16% Propofol
6% Nitrous oxide

Sedation frequency:

65% 0–5 times per month
21% 6–10 times per month
9% 11–20 times per month
5% More than 20 times per month

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Note: 21% of pediatric hospitals who provide sedation work on a sedation service. Their frequency of providing sedation was evenly distributed across all monthly sedation frequencies.

Location of sedations:

86% Inpatient wards
24% Radiology departments
16% Sedation centers
8% Emergency departments
5% Pediatric intensive care unit (PICU)
4% Others: endoscopy suites, Electroencephalograms (EEG), ambulatory surgery and infusion centers

Sedation training:

79% On the job
71% Residency training
44% Training under direct supervision
42% Post-residency CME
19% Operating room (OR)

Training Hospitalists to Provide Moderate and Deep Sedation

There are no national standards for the training of nonanesthesiologists in the practice of safe delivery of sedation. The training should be established locally, and once established it should be adhered to. The training should include evaluation of patients, establishing safe systems of care, decision-making on the most appropriate drugs, and ability to rescue patients from deeper levels of sedation than intended. There are different types of training that hospitalists use to obtain these skills. It is up to the individual hospitalist providing sedation to feel comfortable in their abilities to provide sedation, and it is up to the institutions where these hospitalists work to define the level of training necessary to develop and maintain sedation skills.

On-The-Job Training

Most hospitalists who provide sedation stated they received on-the-job training. The intensity of this training varies widely, from being involved in a few sedations prior to performing them independently, to very structured programs. It is important that hospitalists have defined training prior to performing sedations and are never placed in a position of performing sedations simply because no one else is willing to.

Residency Training

Exposure to and training for safe sedation practice is highly variable during pediatric residencies. Many pediatric residents have significant exposure, and many pediatric residents perform sedations under direct supervision of pediatric-trained attendings. However, since the training is so highly variable, it should not be assumed that most pediatricians have adequate training in residency to perform sedations independently without further training and experience.

Training Under Direct Supervision

This is really part of on-the-job training but implies a more detailed and comprehensive program of gaining experience in safe sedation practice. This training can be done with anesthesiology staff or pediatricians with significant experience and proficiency in sedation. The number of directly supervised sedations and number performed with each drug used should be determined by the local institution.

Operating Room Time

This can be an important adjunct to other types of training. In the operating room (OR), there will likely be opportunities for airway management that are difficult to obtain elsewhere. This is particularly important with the concept of rescue. Most patients in the OR need advanced airway management. Skills that can be practiced in the OR include maintaining airways with positioning, positive pressure ventilation with a bag, laryngeal mask airway (LMA) placement, and intubation. OR time allows improvement of airway management skills in a controlled environment. This type of training is not essential for everyone that is providing sedation but is something that should be strongly considered.

Simulation Time

There are an increasing number of simulation labs available for use in sedation training, particularly in academic medical centers. Training in a simulation lab can be very helpful in training for sedation. Mannequins are becoming more and more sophisticated and are more closely simulating real-life experiences. Simulation labs can be particularly helpful with management of difficult situations that are hopefully avoided in safe sedation practice on actual patients. This training is still somewhat limited and not available to many.

Pediatric Advance Life Support Training

Pediatric Advance Life Support (PALS) training is an important adjunct to the provision of safe sedation. However, it should not be used as a proxy for adequate training for those that are providing sedation. PALS should be a part of a training program for safe sedation, but should never be used alone as an adequate indication of sufficient training to provide moderate and deep sedation.

Ongoing Competency

Once a hospitalist has been trained and credentialed in the provision of safe sedation, it is important to maintain skill and to have a method for measuring those competencies. There are no set standards for the number of sedations to be completed on an annual basis to maintain competencies. Each institution should establish a minimum number and type of sedations performed on an annual basis or should develop a program that includes other methods of maintaining skills, such as OR time or simulation lab time. Some drugs, such as propofol, should have very defined minimum numbers of annual sedations provided by each provider to maintain credentialing. At St. Louis Children's Hospital, nonanesthesiologist providers who are credentialed to use propofol are required to document 25 propofol sedations on an annual basis. This number is not meant to be a guide for others but is an example of one institution's decision.

Credentialing Hospitalists to Provide Moderate and Deep Sedation

Most pediatric hospitalists have completed 3 years of pediatric training in a categorical pediatric residency. Some pediatric hospitalists have finished a combined residency in Pediatrics and Internal Medicine, and a few have completed family medicine residencies. Many pediatric residents have some exposure to the provision of moderate and deep sedation during their pediatric residency, but the provision of moderate and deep sedation is not part of the core competencies as recognized by the Accrediting Council on Graduate Medical Education (ACGME). The training during pediatric residencies in sedation is highly variable, from very little formal training to several dedicated weeks in the OR and on a sedation service. Training and experience with moderate and deep sedation is part of the core ACGME fellowship competencies for pediatric emergency medicine and pediatric critical care medicine.

Each hospital should develop its own criteria for credentialing physicians for the provision of moderate and deep sedation. The joint commission suggests that all individuals who provide moderate and deep sedation have a minimum level of competency based on education, training and experience [2]. The Joint Commission outlines the following abilities and competencies for performing moderate and deep sedation:

1. Ability to evaluate patients before performing moderate and deep sedation.
2. Ability to perform a moderate and deep sedation, including resuscitation of patients who move into a deeper-than-desired level of sedation or analgesia.
   (a) Individuals providing moderate sedation are qualified to rescue patients from deep sedation and have the ability to manage a compromised airway and to provide adequate oxygenation and ventilation.

(b) Individuals providing deep sedation are qualified to rescue patients from general anesthesia and are able to manage an unstable cardiovascular system as well as a compromised airway, and to provide adequate oxygenation and ventilation.

Joint commission standards also require that "individuals administering moderate and deep sedation are qualified and have the appropriate credentials to manage patients at whatever level of sedation is achieved, either intentionally or unintentionally."

It is up to individual institutions to develop credentialing standards for moderate and deep sedation. Credentialing standards for physicians are set through an organized medical staff structure in most hospitals. This is done through the medical staff bylaws and rules and regulations of the hospital. Many hospitals depend on their anesthesiology departments to establish the credentialing rules for the provision of moderate and deep sedation by nonanesthesiologists. The amount of education, training, and experience to provide privileges for the provision of moderate and deep sedation is an institution-by-institution decision.

Table 11.1 outlines the education, training, and experience necessary for moderate and deep sedation privileges at St. Louis Children's Hospital. It also outlines the experience and training necessary for the nonanesthesiologists that provide scheduled sedations on the sedation service. It also outlines the requirements for hospitalists to be granted specific privileges for the use of propofol. This information is presented as an example, and it is one that may not be applied

Table 11.1 Credentialing requirements for hospitalists providing moderate and deep sedation

Credentials Required for all Non-Anesthesiologist Medical Staff	
Successful completion of a post graduate residency training program, approved by either the accrediting Council for graduate medical education (ACGME), the American Osteopathic Association (AOA), or the American Association of Dental Schools (AADS) with exposure to anesthesia and IV moderate and deep sedation including training in indications, contraindications, pre-sedation assessment, intra-sedation care, procedure monitoring, post-sedation care and the pharmacology of sedation medication with associated reversal and resuscitative drugs - **OR –** If post graduate training did not include exposure to anesthesia and sedation as stated above, demonstration of completion of an approved training sequence including both didactic and practical components that meet SLCH requirements and have documented clinical experience for at least 20 cases over the past 12 months with document and quality outcomes that meet guidelines as established by the anesthesiologist-in-chief and St. Louis Children's Hospital medical staff - **OR –** Performed at least 40 documented sedations over the prior 12 months at St. Louis Children's Hospital with documented quality outcomes that meet guidelines as established by the anesthesiologist-in-chief and St. Louis Children's Hospital	
Credentials Required for Hospitalists on Sedation Service	**Credentials Required for Propofol-certified Hospitalists on Sedation Service**
1) St. Louis Children's Hospital moderate and deep sedation privileges	1) St. Louis Children's Hospital moderate and deep sedation privileges
2) Minimum of 1 year experience in SLCH/WU hospitalist program	2) Minimum of 2 years experience in SLCH/WU hospitalist program
3) Track record of strong clinical and interpersonal skills	3) Minimum of 1 year on our sedation service
4) Five OR training days, including bag valve mask ventilation, LMA placements, and intubation	4) Didactic course and simulation lab time as directed by the Department of anesthesiology
5) Documented experience with each sedative agent that will be used in our experience. Including but not limited to ketamine, fentanyl/midazolam, dexmedetomidine, nitrous oxide, pentobarbital, chloral hydrate	5) Ten OR training days, with a minimum of 25 and to patients 15 LMA placements and 15 bag valve mask ventilations
	6) 25 directly supervised propofol sedations

Source: Courtesy of St. Louis Children's Hospital

easily to other institutions; it is not meant as a standard to which other institutions should apply their credentialing process.

Logistics of Setting Up a Hospitalist-Run Sedation Service

Staffing

The number of hospitalists needed to provide sedation services will vary depending on the need that they are meeting. While some pediatric hospitalists provide sedation services full-time, most involved in sedation services do it as one of several clinical responsibilities. The number of hospitalists needed to provide a sedation service needs to account for this, as well as the need to maintain a minimum number of sedations performed on an annual basis for competency. In general, pediatric hospitalists should perform a minimum of 50–100 sedations per year to maintain skills. With less than 50 sedations per year, there should be a rigorous plan for further OR time, simulation time, and supervised time. Further OR time and simulation time is also an important part of maintaining skills for pediatric hospitalists who are performing more than 50 sedations per year.

Staffing Example

Providing a pediatric hospitalist for sedations 5 days/week, 10 h/day requires about 1.5 full-time equivalents (FTE) to staff the service. Therefore, if each pediatric hospitalist provides 4–5 days/month on a sedation service, four pediatric hospitalists would be needed to staff the service. Four to five days per month of providing sedation generally establishes a good balance between maintaining sedations skills and the other skills important to the clinical responsibilities of a pediatric hospitalist.

Sufficient time needs to be planned for training prior to starting a sedation service. It is important to plan for OR time, supervised sedation time, and any other activities involved in training. If you underestimate the amount of time that will take to establish a program, the start date will be delayed and promised expectations may not be met. It is also important to plan for turnover of staff. It is a good idea to get commitment of pediatric hospitalists for a prolonged period after the training while recognizing that some turnover is inevitable. Training of new personnel takes time and other resources that need to be accounted for in the planning stages.

Triaging Patients to Sedation by Pediatric Hospitalists

In general, pediatric hospitalists who are trained and credentialed to provide sedation do so on patients with mild sedation risk. Sedations performed by most pediatric hospitalists do not include planned airway intervention. It is essential that pediatric hospitalists have the ability to rescue patients from a deeper-than-intended level of sedation. Most often, this includes skills of effective positive pressure ventilation and direct airway management through the LMA placement or endotracheal tube placement. Patients must be properly triaged so that those with increased risk from sedation have the proper personnel attending the sedation. At St. Louis Children's Hospital, the following conditions are referred to anesthesiologists for consultation:

- Postgestational age of less than 50 weeks
- Evidence of sleep apnea
- Tracheostomy
- Anatomical airway abnormality
- Cardiac abnormalities leading to decreased cardiac output
- Pulmonary hypertension
- Implanted pacemakers
- Persistent vomiting
- G-tube present
- Swallowing difficulties
- Chronic kidney disease
- Sickle cell disease with complications
- Frequent seizures
- Cerebral palsy with respiratory compromise or airway abnormalities
- Combative behavior
- Significant congenital syndromes

This list is not meant to be comprehensive or complete. All patients should be carefully evaluated for the risk of needed airway intervention and the ability to intervene. If there are any concerns about higher than usual risks, consultation with an anesthesiologist is recommended. Pediatric hospitalists providing sedation should be comfortable and have experience with rescue from complications of sedation, but should refer to others patients who are high risk for complications.

How and When Workups Are Performed for Triage

Pediatric Hospitalists provide sedations independently and may also be asked to supervise sedations performed by others, including nurses. The responsibility for evaluation of patients undergoing sedation belongs with the supervising hospitalist when one is performing the procedure personally and when supervising someone else. Rules and regulations vary by hospital, but in most cases the sedating or supervising physician needs to perform a pre-sedation evaluation. This is not meant to replace a requirement for a pre-sedation physical exam performed by the ordering physician. This exam is meant to be focused on the risks a performing a scheduled sedation. This exam needs to be scheduled with ample time prior to the scheduled sedation. It is important to have the space and equipment to properly perform this exam. This exam is essential to the final decision-making of how and whether to proceed with a sedation. This exam is also essential in determining whether the sedation should proceed under the guidance of a pediatric hospitalist or whether it is best done by an anesthesiologist. Complication rates can increase when there is not ample time to evaluate patients immediately prior to sedation.

For elective sedations that allow performance of a test or procedure that is needed but not urgent, safety standards (including NPO times) should be carefully followed. If issues are found at the time of a pre-sedation exam, the sedation should be rescheduled unless rescheduling could increase risk to the patient. The risks of proceeding must be carefully measured against the risk in delaying diagnosis or treatment. At St. Louis Children's Hospital, the following are minimum recommendations for rescheduling elective sedations:

- Asthma without underlying infectious etiology – 7 days
- Asthma with infectious etiology – 3 weeks
- URI with cough or congestion – 3 weeks
- Fever – when back to normal and off antipyretics 24 h
- Vomiting – when ceased for 24 h and tolerating clear liquids and evidence of good hydration
- Croup – 3 weeks
- Pneumonia – 4 weeks
- Influenza – 3 weeks
- RSV – 6 weeks

These are meant as general guidelines and not as absolute rules. This is one hospital's guidelines and does not mean that other guidelines are not valid. If the urgency of sedation requires that the test or procedure be performed in the presence of one of the above conditions, consultation with an anesthesiologist is generally recommended.

Funding Pediatric Hospitalist Sedation Programs

Pediatric hospitalist sedation programs are generally funded from two sources: (1) physician professional fees and (2) financial support from hospitals. Depending upon the number of sedations done, the ability to bill anesthesia codes, and reimbursement percentage, the level of funding of pediatric hospital sedation programs varies from institution to institution. The Centers for Medicare and Medicaid (CMS) determines most rules in regard to physician billing [3]. CMS rules require that sedation services are overseen by a hospital's anesthesiology division/department. This generally requires a close working relationship between a hospital's anesthesiology group and others providing moderate and deep sedation. Most sedations performed reach the level of "deep sedation" as defined by the American Society of Anesthesiologists and the American Academy of Pediatrics [4, 5]. In most

cases, anesthesia codes can be used. Anesthesia codes are used appropriately by nonanesthesiologists when the level of care provided meets the standard of those codes. Ability to use anesthesia codes varies across USA, sometimes on a state-by-state or local basis. Anesthesia codes are most often successfully billed when there is agreement within an institution about the appropriate use of these codes by nonanesthesiologists. If there is disagreement among departments of a hospital, it is often difficult to get reimbursed for these codes. Separate codes for moderate sedation were developed in 2006. These do not have Relative Value Units (RVUs) attached. Each institution is responsible for determining the charges for these codes. Success in reimbursement for moderate sedation codes varies from region to region.

If pediatric hospitalist sedation programs have scheduled sedations each day, it is likely that the cost of providing this service will be met through the billing and collection of physician professional fees. If a sedation program is responsible to meet urgent demand and thus not able to schedule a full day, there is likely to be a shortfall in meeting the cost of the program. The ability to provide timely, safe sedation is important to many hospital services. Radiology, surgery, inpatient services, and outpatient services all benefit from this. Hospital administration and some services independently will likely be willing to provide financial support of sedation services outside of profession billing. It is important to understand who benefits from efficient sedations and to use that in negotiating support for those services.

The Future of Hospitalist Sedation Services

Based on estimates from the Society of Hospital Medicine, American Academy of Pediatrics, and Academic Pediatric Association, the number of pediatric hospitalists is 2,500–3,500 in USA. In a survey of pediatric hospitalists, 54% report providing moderate and deep sedation [1]. Pediatric hospitalists can be a resource to meet the increasing demand for sedation. Exposure to safe sedation practices and training in safe sedation is becoming more common in pediatric residencies. It is likely that the need for sedation services will grow and also that the number of pediatric hospitalists will grow. Thus, it is likely that the number of pediatric hospitalists in sedation programs will grow.

Developing National Standards for Training and Credentialing Pediatric Hospitalists in Sedation

There are currently no national standards for training and credentialing pediatric hospitalists. Core competencies in Pediatric Hospital Medicine have been developed, and providing safe sedation is part of those recommended competencies [6]. As training for hospitalists is standardized, sedation training will likely become part of the standard. Most pediatric hospitalists gain competence for providing sedation after residency. Fifty percent of hospitalists report depending on continuing medical education as part of gaining and maintaining sedation skills. There are national conferences dedicated to pediatric sedation outside the OR. It is likely that a national course in sedation will be developed, but it is unlikely that a standardized training and certification process will emerge within the next few years. Credentialing for sedation will likely remain a local process. There are national organization recommendations about providing sedation, but none yet on the specific training for those providing sedation [4, 5]. It is important that pediatric hospitalists providing sedation receive additional training, maintain skills, appropriately select patients, have the ability to rescue from deeper-than-intended levels of sedation, and work within systems where backup is available.

Planning, Monitoring, and Recovering from a Sedation

It is important for sedation to be performed in the safest possible manner. This begins by identifying that all personnel, equipment, and facilities needed to manage emergencies are immediately

available. The safest place to perform sedation is generally in an area of the hospital where sedations are performed on a regular basis. Personnel in those areas will be familiar with all the equipment needed for monitoring and potential rescue, and will have some experience to assist if necessary. If sedation is performed in an area of the hospital where sedation is not common, it is essential that the sedation provider have all necessary materials and personnel available before a sedation proceeds.

Pre-sedation Evaluation

All children undergoing sedation should be carefully screened for the potential of adverse events during sedation and recovery. A focused pre-sedation history and physical should be performed by the sedation provider. This evaluation should focus on characteristics that would indicate increased risk of sedation for the patient or the potential for difficult airway management. The history should include previous problems with sedation or anesthesia, stridor, snoring and sleep apnea, and recent respiratory illness. Significant physical exam findings include significant obesity, short neck, small mandible, dysmorphic facial features, small mouth opening, and large tonsils.

If a patient has significant history and physical exam findings indicating increased risk of providing sedation, the risks of providing the sedation need to be weighed against the absolute need for the procedure or diagnostic study. A hospitalist performing sedation should always feel comfortable providing rescue from a stage of sedation deeper than that intended to perform the procedure. If airway problems are anticipated, or are not anticipated but would be difficult to manage because of a patient's anatomy, consultation of an anesthesiologist is recommended.

The patient physical exam status endorsed by the ASA can be useful in assessing sedation risk. ASA class I and II children are at low risk for adverse events during sedation when carefully monitored. ASA III patients are by definition at increased risk. In general, for urgent hospital based sedations most hospitalists, should provide sedation only to ASA class I and II and patients. Before providing sedation to ASA class III patients, consultation with anesthesiology is advised. Hospitalists working on a sedation service or providing sedation regularly can provide sedation to ASA class III patients safely, as long as those patients are carefully evaluated and a backup system of care has been planned and is in place.

There is no proven relationship between fasting time prior to sedation and the risk of aspiration in humans. The general opinion is that fasting will likely reduce the risk of aspiration. For elective procedures, individual hospital guidelines for fasting should be followed just as they would be for general anesthesia. For urgent procedures, patients should be fasted as soon as the possible need for sedation is identified. The risk of clinically significant aspiration is small for most patients, but needs to be weighed carefully against the need to perform a diagnostic or therapeutic procedure quickly.

Personnel

For moderate sedation, a provider with adequate sedation training and experience needs to be responsible for the sedation and analgesia. This person may also perform the procedure. A second person with knowledge in basic pediatric life support is also required. This person is responsible for monitoring the patient's cardiopulmonary status. This person is also generally responsible for recording the data in a sedation record and may assist in brief, interruptible tasks once the level of sedation is stabilized.

For deep sedation, a provider trained in advanced pediatric life support must be in the room. The provider of the deep sedation should provide direct monitoring of the patient and must not be primarily responsible for the procedure. Problems with ventilation and oxygenation during deep sedation are generally easily managed when rapidly recognized. Deeper-than-intended sedation may occur in any patient; it is generally recommended that the sedation provider be prepared to manage deep sedation even when moderate sedation is expected and general anesthesia when deep sedation is intended.

Monitoring

For moderate sedation, a minimum of pulse oximetry is strongly recommended. In addition, continuous monitoring of heart rate, respiratory rate, and intermittent noninvasive blood pressure measurements are recommended. If intravenous access is not otherwise established, it is not required, but should be carefully considered.

For deep sedation, continuous ECG heart rate, respiratory rate, pulse oximetry, and noninvasive blood pressure monitoring are strongly recommended. If available, end tidal CO_2 capnography monitoring is also recommended. Intravenous access for patients receiving deep sedation is also recommended. Monitoring is recommended throughout the sedation and recovery. In addition to electrophysiological monitoring, the child's color, airway patency, rate and depth of respiration should be monitored by direct patient observation.

Medications

Medications used to provide moderate and deep sedation should be carefully chosen by the sedation provider to meet the goals of sedation. There can be many reasonable approaches to safe sedation and analgesia of patients. The goal of sedation should be to use the lowest dose and number of drugs with the widest therapeutic index. It is probably best for hospitalists to become familiar with a minimal number of drugs to provide pain relief and motionless sedation. These drugs may vary from provider to provider based on experience and availability. It is better to be comfortable with a small number of drugs that fit most circumstances than to use a large number of drugs to try to fit every clinical situation. In general, ketamine for painful procedures or for short motionless procedures and pentobarbital for long motionless, painless procedures will meet most needs for sedations that a hospitalist provides. Dexmedetomidine may be a reasonable alternative for pentobarbital. There may be instances when sedation is best provided with a drug for which the hospitalist is uncomfortable or unfamiliar. In those cases, referral of the patient to another sedation provider is probably more prudent than proceeding with a drug that one uses infrequently.

Final Checklist Prior to Sedation

Just prior to the sedation, the sedation provider should go through a final checklist. This checklist should include a timeout, with patient identification and recheck of the patient's weight. The SOAPME acronym can be a useful tool for this final checklist.

Suction: Equipment on and tested with properly sized Yankauer Catheter.

Oxygen: Nasal cannula, CPAP bag available and hooked up, functioning ball supply and oxygen tank if transporting patient.

Airway: Size-appropriate nasopharyngeal and oral pharyngeal Airways, endotracheal tubes (ETTs), laryngeal mask airways (LMAs), functioning laryngoscope blades.

Pharmacy: Medications for sedation. Emergency medications for intubation. Reversal agents if using opiates or benzodiazepines.

Monitors: Pulse oximetry, NIBP, end tidal CO_2 capnography, ECG. Available stethoscope.

Equipment: Crash cart/airway cart available nearby and other special equipment anticipated.

Recovery

It is important that patients be monitored and fully recovered from sedation prior to discharge home or placement back in an inpatient bed. Monitoring of recovery should be done by trained and experienced personnel familiar with the recovery phase of sedation. Hospitalists may need to do this themselves if properly trained nursing resources are not available. Patient handoffs should occur only if there are protocols in place for discharge or transfer by nonphysicians.

Some medications used for sedation have extremely long half-lives. Chloral hydrate and pentobarbital are two such examples. Patients may seem to be nearly recovered with these medications and then have episodes of significant resedation with

potential airway compromise. Prolonged periods of recovery are necessary for safe discharge when using drugs with a long half-life.

Discharge/Transfer Criteria

All these criteria should be met prior to discharge or transfer to another unit:

1. Vital signs at baseline
2. No respiratory distress
3. SPO_2 at baseline
4. Function at baseline; sits or stands with minimal assistance
5. Hydration normal with no emesis or significant nausea
6. Aldrete recovery score ≥9 for discharge or ≥8 for admission
7. Pain score ≤4 for discharge or ≤6 for transfer to inpatient bed
8. Patient is awake and attentive or very easily aroused

Aldrete Recovery Score (need score of 9 for discharge/8 for admission)*

- Activity
  Able to move 4 extremities voluntarily or on command = 2
  Able to move 2 extremities voluntarily or on command = 1
  Able to move 0 extremities voluntarily or on command = 0
- Respirations
  Able to breathe deeply and cough freely = 2
  Dyspnea or limited breathing = 1
  Apneic = 0
- Circulation
  BP ± 20% of pre-sedation level = 2
  BP ± 20–50% of pre-sedation level = 1
  BP ± 50% or more pre-sedation level = 0
- Consciousness
  Fully awake = 2
  Arousable with verbal stimulation = 1
  Not responding = 0
- Color
  Pink = 2
  Pale, dusky, blotchy, jaundiced = 1
  Cyanotic = 0

* Aldrete Recovery Scale may be supplanted by another established discharge scale (refer to Chapter 4).

Sedation Drugs (Table 11.2)

Commonly used sedative, analgesic and hypnotic agents will be outlined from the perspective of the hospital medicine specialist.

Ketamine

Ketamine is a very useful drug for short painful procedures and for short periods of decreased motion, as needed by CT. Ketamine can be given IV or IM. When given IV, onset is usually within 30–60 s. When given IM, onset is usually within a few minutes. With a single dose of 1–2 mg/kg IV, initial deep effects last 5–10 min. Repeat doses of 0.5–1 mg/kg can be given at intervals of 5–10 min, based on effect, for longer procedures.

Ketamine given in small doses allows for the preservation of spontaneous respirations, and airway reflexes, while still providing unresponsiveness and analgesia. The relative lack of respiratory depression and sparing of airway reflexes have made ketamine a popular choice for a wide range of painful procedures. By most common definitions, the level of sedation most often achieved is deep. Monitoring and personnel decisions should be based on the patient's likelihood to reach a level of deep sedation.

Laryngospasm is a rare but potentially serious adverse reaction to ketamine. Ketamine is contraindicated in patients with increased intracranial pressure. Ketamine can cause hypertension, tachycardia, significant irritability during emergence, and nystagmus. Glycopyrollate 5 μg/kg IV may decrease oral secretions.

Coadministration with midazolam is a common practice. It has not been found to decrease the incidence of dysphoria or other unpleasant

Table 11.2 Sedation drugs

Drug	Usage/sedation level	Dose	Onset/duration	Coadministration	Precautions
Ketamine	Short painful procedures; short periods of decreased motion; deep sedation to anesthesia	IV: 1–2 mg/kg IM: 2–4 mg/kg Repeat doses of 0.5–1 mg/kg at intervals of 5–10 min, based on effect	IV: Onset 30–60 s IM: Onset 3–10 min Duration 5–10 min deep sedation	Midazolam as anxiolytic prior to ketamine administration has not been found to decrease incidence of dysphoria or other unpleasant emergency phenomenon	Laryngospasm (rare); contraindicated in patients with increased intracranial pressure Can cause hypertension tachycardia, significant irritability during emergence, nystagmus in most patients; glycopyrollate 5 μg/kg IV may decrease oral secretions
Fentanyl and midazolam	Combination provides analgesia and sedation for short painful procedures; moderate to deep sedation	Midazolam 0.1 mg/kg IV with subsequent doses of 0.05 mg/kg every 2–5 min until desired effect; fentanyl 1–2 μg/kg IV with subsequent doses of 1 μg/kg every 2–5 min to desired effect	Fentanyl IV: Onset 30–60 s; duration 5–10 min Midazolam IV: Onset within 1 min, peak in 2–6 min; duration 30–60 min Midazolam PO: Onset 15–20 min; duration 60–90 min	Midazolam is generally given first and titrated to provide anxiolysis to moderate sedation. Fentanyl is then added for analgesic effect and moderate to deep sedation	Can cause respiratory depression disproportionate to sedation level; patients should be closely monitored for obstruction and apnea
Nitrous oxide	Analgesic and amnestic effect Moderate sedation when given alone Moderate to deep sedation when combined with other agents	30–70% nitrous oxide mix with oxygen by inhalation		May be combined with oxycodone 0.2–3 mg/kg to max of 20 mg. This combination can result in deep sedation	
Pentobarbital	Long-term motionless sedation when pain control is not an issue	IV: 2.5–7.5 mg/kg. Can be given as initial dose of 2.5 mg followed by increments of 1.25 mg/kg until desired effect		Midazolam (0.05 mg/kg to max of 5 mg) to augment sedation and decreased motion	Prolonged postsedation recovery period due to long half-life. Prolonged irritability up to 24 h

(continued)

Table 11.2 (continued)

Drug	Usage/sedation level	Dose	Onset/duration	Coadministration	Precautions
Propofol	Deep sedation to general anesthesia; can be used for short procedures needing deep sedation or prolonged motionless sedations	1–2 mg/kg followed by 1 mg/kg as needed for movement every 5–10 min for short procedures; for prolonged painless sedation, 1–2 mg/kg bolus, then as infusion of 150–200 μg/kilo/min	Onset <1 min/duration for single dose 5–10 min	Opioid or other pain medication if pain is likely	Should only be administered by experienced providers with advanced airway skills and significant experience with propofol. Airway obstruction and/or decreased respiratory effect is common; attention to airway is essential
Choral hydrate	Best for motionless sedation of children <12 months of age	25–100 mg/kg orally or rectally to max of 3 g	Onset 30–60 min; recovery 60–120 min		Respiration depression and hypotension; due to half-life of 4–9 h, special precautions should be taken regarding discharge
Dexmedetomidine	Sedation	Bolus: 1–3 μg/kg infused over 10 min Infusion: 1–2 μg/kg/h	Onset by end of bolus delivery	Midazolam 0.05 mg/kg up to 2 times or pentobarbital 2 mg/kg to increase success of scan completion and safety	Bolus dose: Bradycardia, sinus arrest, transient hypertension Infusion dose: hypotension, bradycardia; precaution needed for hypovolemia patients, patients receiving vasodilators or negative chronotropic agents, patients with arrhythmias, renal or hepatic insufficiency, and chronic hypertension

recovery phenomenon. Midazolam, however, may still be useful as an anxiolytic prior to the administration of ketamine.

Dosing:

Ketamine IV: Dose 1–2 mg/kg. Repeat doses of 0.5–1 mg/kg every 5–10 min as needed. There is no absolute upper limit of ketamine, but other methods of sedation should be considered for procedures lasting more than 30–45 min.

Ketamine IM: Dose 2–4 mg/kg. Onset 3–10 min.

Fentanyl and Midazolam

These drugs are often used in combination to provide analgesia and sedation. Midazolam and fentanyl when combined will most often lead to moderate-to deep-sedation. Personnel and monitoring decisions should be based on the likelihood deep sedation will be reached. Fentanyl/midazolam can cause respiratory depression that is out of proportion to the level of sedation achieved. Patients must be closely monitored for obstruction and apnea when these drugs are used in combination. These drugs have the advantage of being able to be titrated to effect.

Fentanyl is a high potency opioid that has minimal adverse hemodynamic effects. Onset of action is 30–60 s, and duration of action is 5–10 min. The major side effect is respiratory depression that is dose-related but sometimes can occur with low doses. The risk of respiratory depression is higher with benzodiazepines and barbiturates. Hypertension and chest wall rigidity are rare adverse events but can be difficult to deal with.

Dosing:

Midazolam: 0.1 mg/kg IV with subsequent doses of 0.05 mg/kg every 2–5 min to reach desired effect.

Fentanyl: 1–2 μg/kg IV with subsequent doses of 1 μg/kg every 2–5 min to reach desired effect.

Midazolam is often administered first with the goal of achieving anxiolysis to moderate sedation. This generally requires 0.1–0.2 mg/kg. Fentanyl is then added for analgesic effect and to achieve moderate to deep sedation.

Nitrous Oxide

Nitrous oxide when inhaled as a 30–70% mix with oxygen can produce dissociative euphoria, drowsiness, anxiolysis, and moderate amnesia and analgesia. Onset of effect is usually 2–3 min and recovery is complete 3–5 min after stopping inhalation. Children receiving nitrous oxide at 30–70% are usually moderately sedated; a combination of nitrous oxide with a benzodiazepine or an opioid may cause deep sedation or even general anesthesia. Some children seem not to respond to nitrous oxide, probably due to psychological resistance. Vomiting occurs in about 10% of patients receiving nitrous oxide. Nitrous oxide causes gas-filled cavities to expand; its use should be avoided if possible bowel obstruction, pneumothorax, or otitis media are suspected.

When nitrous oxide is used as a sole agent, monitoring should be at the level required for moderate sedation. If used with an oral opioid such as oxycodone (0.2–0.3 mg/kg, maximum 15 mg), deep sedation can sometimes be achieved and monitoring should be at the level required for such.

Special equipment is required for delivery of nitrous oxide. There are commercially available models with a mask, but effective nitrous oxide delivery requires a good mass seal and a patient generating significant negative pressure. Young patients may not be able to generate enough negative pressure to overcome the fountain nitrous apparatus. Nitrous oxide for dental use is commercially available, but delivery of nitrous oxide through the nasal cone may limit its use in medical settings. Institutions that have reported significant success with nitrous oxide often have internal support from their biomedical department.

Dosing:

30–70% nitrous oxide mix with oxygen by inhalation. May be combined with oxycodone 0.2–0.3 mg/kg, max. 15 mg. This combination can result in deep sedation; sedation providers need to be prepared for such a result.

Pentobarbital

Pentobarbital is a moderately long-acting barbiturate with sedative hypnotic effects but no analgesia.

The onset of action occurs in less than 60 s when given intravenously and after 10–30 min when given IM or PR. Recovery is dependent on redistribution and occurs in 50–75 min, even though the half-life is 15–20 h. Respiratory depression has been associated with pentobarbital and is dose dependent.

Pentobarbital has been shown to be highly effective for long-term motionless sedation when pain control is not an issue. Pentobarbital generally results in deep sedation. Airway reflexes and breathing are generally not significantly diminished. Monitoring, however, should be for the anticipated level of deep sedation and personnel with advanced airway skills should be available.

Midazolam given intravenously (0.05 mg/kg, maximum 5 mg) can be given if there is sustained motion.

The postsedation period can be prolonged. It is important to give the patient adequate time to recover. Sometimes patients can be stimulated to the level of a wakefulness that supports discharge, and caregivers need to realize that there can be resedation because of the long half-life of pentobarbital. Patients often have prolonged irritability, sometimes lasting up to 24 h.

Dosing:
Pentobarbital IV: 2.5–7.5 mg/kg. This can be given as an initial dose of 2.5 mg/kg followed by increments of 1.25 mg/kg until sedation is achieved.

Midazolam IV: 0.05 mg/kg, maximum 5 mg. Can be used to augment sedation and decreased motion.

Diprivan (Propofol)

Propofol is a nonbarbiturate sedative hypnotic agent. It has no analgesic effect. Propofol is administered intravenously, has an onset of less than 1 min and the duration of action for a single dose is 5–10 min. It can be used in doses of 1–2 mg/kg to provide sedation for short procedures. If pain is likely, propofol needs to be given with an appropriate dose of an opioid or other pain medication. For prolonged painless sedation, as is needed for MR scans, it can be given as a 1–2 mg/kg bolus, then as an infusion of 150–200 μg/kg/min. The quick onset of action and short duration make propofol an attractive drug for brief procedures; however, it can be difficult to titrate and it is easy to overshoot the intended level of sedation leading to apnea and hypotension.

Propofol should only be administered by experienced providers with advanced airway skills. Propofol leads to deep sedation or even a general anesthesia level. Significant numbers of patients will have airway obstruction and/or decreased respiratory effect when given a bolus of 1–2 mg per kilo of propofol. Attention to airway is essential.

In general, propofol should only be considered by providers that have significant skills and experience with deep sedation, with advanced airway skills, including placement of LMAs and intubation.

Dosing:
Prolonged sedation: 1–2 mg/kg initial bolus followed by 150–200 μg/kg/min.

Short procedures: 1–2 mg/kg followed by 1 mg/kg as needed for movement every 5–10 min.

Chloral Hydrate

Chloral hydrate is a halogenated hydrocarbon selected for hypnotic effects but has no analgesia. The drug has a half-life of 4–9 h and generally produces sedation within 15–30 min, with recovery by 60–120 min. Significant side effects include respiratory depression and hypotension. Its effects can be highly variable. The drug has best success when motionless sedation is needed for children less than 12 months of age.

Chloral hydrate has a long half-life. Special precautions should be taken in evaluating patient for discharge. Resedation after discharge has been documented. Patients that are discharged too early are at risk for airway obstruction. Sufficient time after the last dose of chloral hydrate should have passed before discharge.

Dosing:
25–100 mg/kg administered orally or rectally, maximum dose 3 g total.

St. Louis Children's Hospital protocol: children 4–6 months of age 50 mg/kg PO/PR;

additional 25 mg/kg after 30 min if needed. Children 6–12 months of age: 75/kg PO/PR; additional 25 mg/kg after 30 min if needed.

Dexmedetomidine

Dexmedetomidine is a selective alpha-2 receptor agonist. It has sedative, analgesic, and antishivering properties. It is approved by the Food and Drug Administration (FDA) as a sedative but does not have a pediatric labeling. EEG activity while being sedated with dexmedetomidine resembles natural stage 2 sleep, consistent with non-REM sleep [7].

Dexmedetomidine has an initial half-life distribution of 6 min with terminal half-life of 2 h. Adverse reactions associated with a bolus dose include bradycardia, sinus arrest, and transient hypertension. Adverse reactions associated with infusion dose include hypotension and bradycardia. Precautions should be taken for hypovolemia patients, patients receiving vasodilators or negative chronotropic agents, patients with arrhythmias, patients with renal or a hepatic insufficiency and with chronic hypertension [8].

Personal experience suggests that patients receiving dexmedetomidine for prolonged motionless sedation sometimes are sensitive to loud noises such as occur in a MR scan. Ear plugs may be helpful. Midazolam, ketamine, propofol, or pentobarbital may be effective adjuncts to increase the efficacy of dexmedetomidine sedation [9–17].

Dosing:
Bolus: 1–3 μg/kg infused over 10 min. Patients generally become sleepy after a few minutes and are generally able to begin the procedure when a bolus is done.

Infusion: 1–2 μg/kg/h. Please note that this infusion is per hour, not per minute.

Midazolam given to supplement sedation: 0.05 mg/kg may be given up to 2 times.

Pentobarbital given to supplement sedation: 2 mg/kg

Case Studies

Case 1

A 20-month-old male was admitted to the hospital with a history of lethargy and fever. Lumbar puncture in the emergency department obtained bloody fluid. The patient was begun on antibiotics and admitted to the hospital. A CT scan was obtained in the emergency department, without sedation. It appears to be normal. A repeat lumbar puncture has been ordered. The patient is now improving and is much more active than on admission. It is thought that the success of lumbar puncture will be improved if done with sedation.

The patient was previously healthy and has had some URI symptoms in the past week but no respiratory distress. The patient has no history of asthma, pneumonia, or other respiratory symptoms. He has occasional mild snoring, particularly when he has a URI. He has not been snoring the past few nights.

Physical exam reveals an alert, active but mildly irritable 20-month-old male with enlarged tonsils, normal-shaped jaw, and normal cardiorespiratory exam.

***Considerations*:** An adequate sample of cerebral spinal fluid would help with diagnosis and length of treatment decision. Without an adequate CSF sample, the length of antibiotic therapy and hospitalization may be significantly increased. The risk of sedation needs to be carefully assessed. The risk may be increased because of his recent URI, febrile illness, large tonsils, and a history of mild snoring. The urgent need for the test needs to be weighed against the potential increase in the risk of sedation. The hospitalist involved

in the patient's care is currently credentialed to provide moderate and deep sedation in the hospital and decides to proceed.

The first consideration is the location of sedation. There is a treatment room on the inpatient floor. In the treatment room are an oxygen supply, suction, and the cardiorespiratory monitor, including pulse oximetry. There is a nurse available and a nursing technician to help with the sedation and procedure. The nurse is assigned to monitor the patient while the sedating physician performs a lumbar puncture. The nursing technician will help hold the child while sedation is being performed.

Once the pre-sedation evaluation has been performed, proper personnel are available, and proper monitoring equipment is available, the best pharmacological method for sedation is determined.

Sedative Agents: Options and Considerations: *Ketamine*: A short acting potent analgesic and sedative agent. It has the advantage of being administered either IM or IV. It is generally airway-sparing. By most commonly used sedation level definitions, it leads to deep sedation. There is some concern for transient increase in blood pressure with potential increases in intracranial pressure. These concerns must be carefully weighed against the efficacy and safety of ketamine.

Midazolam/fentanyl: Together, this benzodiazepine and opioid cause potent sedation and analgesia. Airway obstruction and hypopnea occur in some patients with this combination. Usually, simple airway maneuvers including a chin lift or jaw thrust are all that is necessary. The level of sedation achieved depends on the amount of each drug given, but even with careful titration deep sedation is often the end result. Providers need to be trained and experienced in rescuing patients from a level of deep sedation if necessary.

Nitrous oxide: This can be an effective drug for sedation but does require equipment to deliver the nitrous oxide, including proper scavenging. Nitrous oxide is sometimes given in combination with oral opiates. When this is done, the level sedation achieved is most often moderate but can easily become deep. Patients given nitrous oxide as a sole agent may only need observational monitoring and pulse oximetry, but when combined with other agents should receive the same monitoring as one expecting to achieve deep sedation.

Case 2

A 3-year-old female with mild developmental delay had her first known seizure on the day of admission to the hospital. The seizure was generalized with tonic–clonic movement lasting 20 min. The seizure stopped spontaneously. The patient was evaluated in the emergency department. The patient was back to normal activity about 90 min after the seizure stopped. Workup for infectious etiology was performed. The day after admission, the patient appears to be in a normal state of health. A pediatric neurology consult is obtained; one of the recommendations is an MRI brain.

Other than mild developmental delay, the patient has no other chronic health problems. She has no recent respiratory symptoms or other illnesses. She was in her usual state of health pre- and post-seizure. She has no history of asthma, no history of snoring, no previous sedations, and no family history of problems with sedation. Her physical exam is unremarkable with no indications of any increased risk of sedation.

***Considerations*:** A MRI may be helpful in determining or eliminating significant causes of a generalized seizure. The risk of sedation needs to be carefully weighed against the need for the MRI. While the MRI may direct further evaluation and treatment, it is unlikely to have an immediate impact on care. The MRI for

sedation should be obtained in the safest way possible. The safest sedation is one that is scheduled with proper preparation, during daytime hours, with the optimal number of experienced personnel available. If this can be done during the hospital stay it certainly will be a convenience for the family and will help the physicians that are deciding on a course of treatment. However, if the MRI for sedation can be more safely obtained at a later date even with a return to the hospital, it is probably best to do so. In this case the risk of sedation is likely to be the same at the time of the request for MRI as it will be in the near future. The hospitalist involved in the care of this patient is trained and credentialed in safe delivery of moderate and deep sedation. The hospitalist decides to proceed with sedation after confirming the availability of the MRI scanner and that a nurse is also available.

Sedation can either occur in a separate location from the MRI scanner with transfer into the scanner, or occur in the scanner. In either case, it is essential that the hospitalist ensure that all the proper equipment is functioning and that potential rescue equipment and medications are available. The sedation is best done in an area where the physician and nurse are both familiar and comfortable. Many common monitoring devices, including chest leads, blood pressure cuffs, and pulse oximetry probes, are not compatible with an MRI scanner. Metal-containing equipment can heat up and cause burns. It is essential that MRI compatible monitoring equipment is available.

The hospitalist providing sedation decides to a begin sedation in the MRI scanner. There is proper monitoring equipment, suction, oxygen source, and an airway cart with all potential rescue materials available. In addition to the hospitalist, there is a nurse available.

Sedative Agents and Considerations: *Chloral hydrate*: A long acting oral hypnotic can be effectively used for deep sedation. This drug does not generally cause respiratory depression but can be associated with obstruction. The level of sedation achieved with chloral hydrate is variable; monitoring should be for the potential of deep sedation. This drug is highly effective for children less than 12 months of age, but there are increased rates of failure of adequate level of sedation in older children. It is important to monitor children for sufficient length of time to make sure that they have fully recovered from the medication prior to discharge. Deaths have occurred due to early discharge from this medication.

Pentobarbital: Most commonly given IV and can be given PR or PO. This long-acting barbiturate most often causes a consistently deep sedation. It can be titrated to effect. It is shown to be highly effective and to be safe when used with proper monitoring. There is a high rate a significant irritability in the recovery phase and in the hours after the procedure is performed.

Dexmedetomidine: This sedative agent is most commonly given IV. It is most commonly given as a bolus followed by infusion. Generally, deep sedation is achieved in about 5–10 min with a 2–3 μg per kilo dose and is maintained by a continuous infusion of 1–2 μg/kg/hr. Patients can be stimulated with loud noises so ear protection may be helpful. Patients may sleep for a long period after infusion is stopped. Fewer patients seem to have irritability post-sedation than with other agents.

Propofol: This short acting sedative/anesthetic is given as an infusion IV. It is generally given in a bolus of 1–2 mg/kg. This is associated with a significant rate of airway obstruction and occasional apnea. These problems are transient, but do require proper attention, often including active airway management. While all drugs that result in deep sedation require personnel who are adequately trained in airway management and rescue from deep sedation, propofol requires that the physician administering be very comfortable, trained and experienced with airway management and rescue techniques. The use of propofol by nonanesthesiologists remains a controversial

subject. There is increasing evidence that the use of propofol by well-trained, experienced emergency physicians, intensivists, and hospitalists can be safe when working within systems designed for the safe delivery of sedations.

Case 3

A 3-year-old female is admitted to the hospital with a diagnosis of left thigh cellulitis. Physical exam on the second hospital day reveals increasing size and subcutaneous fluctuance. The diagnosis of abscess is made, and a decision is made to proceed with incision and drainage.

Considerations: The timing of the sedation is important. While incision and drainage of an abscess is urgently necessary, it most often does not require emergent attention. Therefore, hospitalists providing sedation should follow all of their institutional guidelines in NPO status and timing of the sedation. Incision and drainage can be a very painful and often anxiety-provoking procedure. It is possible to do adequate incision and drainage with very little analgesia or anxiolysis, but the patient may have considerable pain and suffering. Sedation and analgesia should be at the lowest level to provide reasonable pain control. Depending on the size of abscess, the age of the patient, and the psychological development of the patient, analgesia and sedation may range from local pain control to deep sedation. The provider of the pain control and sedation should carefully weigh the risks of sedation vs. anxiety and pain associated with no sedation or inadequate sedation.

Sedative Agents and Considerations: *Midazolam and local pain control*: A single dose of midazolam or other benzodiazepine may provide enough anxiolysis that the area of the abscess can be injected with 1% lidocaine in incision and drainage done with little or no discomfort. In general, this technique is more effective with cooperative children and adolescents that have some understanding of what is going to happen. Midazolam, in addition to anxiolysis, has significant amnestic affect. Many times children and adolescents will not remember a mildly painful procedure, even though they seem to have a significant reaction to it.

Ketamine: Given IM or IV, it has significant analgesic and sedative properties. It is given as 1–2 mg per kilo IV or 2–4 mg per kilo IM. The onset is usually 30–60 s IV and several minutes when given IM. Ketamine produces a level of sedation most consistent with deep sedation by standard definitions. Monitoring, personnel, and equipment should be consistent with the same.

Nitrous oxide and oxycodone: The combination of nitrous oxide and oxycodone has been shown to be very effective in controlling pain and anxiety. Nitrous oxide can be given as an inhalation of 50–70%. When nitrous oxide is combined with oral oxycodone to 0.3 mg per kilo (max dose 20 mg), it most often causes a level of sedation consistent with moderate sedation, but can cause deep sedation or in rare cases a level of responsiveness most consistent with general anesthesia. Respiratory drive and airway reflexes are generally very well preserved with this combination, but monitoring consistent with deep sedation is probably most appropriate. Nitrous oxide does require a delivery system which is not available in all hospitals.

Case 4

An 11-month-old with nasopharyngeal rhabdomyosarcoma was referred to the hospitalist-run sedation service for sedation for a bone scan. The patient had been recently diagnosed and the bone scan was ordered as part of the initial staging evaluation. The only symptom of the rhabdomyosarcoma was mild facial swelling. The patient had no difficulty breathing, no snoring, and no history of a respiratory illness. The patient had received an MR scan at an outside hospital under general anesthesia.

***Considerations*:** It is important for diagnostic and therapeutic reasons for this patient to receive a bone scan. Evaluation of the patient is unremarkable except for mild facial swelling. The nasopharyngeal rhabdomyosarcoma, based on MR scan, is not extensive. The patient has no signs of respiratory obstruction. However, because of the prolonged nature of the bone scan, the patient will clearly need deep sedation. During deep sedation, it is unclear the effect the nasopharyngeal growth will have on risk of obstruction and ability to ventilate. For this reason, it is probably best to have the scan performed by personnel that are the most comfortable with airway management including LMA placement and intubation.

***Sedative Options and Considerations*:** Following a discussion with anesthesiology, the hospitalist proceeded with the sedation using propofol. The patient was given 2 mg/kg of propofol and had significant signs of airway obstruction. A chin lift or jaw thrust was performed and the obstruction was relieved but the patient continued to have significant stridor. Constant manipulation of the airway was necessary to maintain it. Anesthesiology backup was notified. The decision was made to abort the sedation and maintain airway until the patient was fully recovered or to have an anesthesiologist take over the case and place a LMA. An anesthesiologist was able to take over the case, propofol was continued, the bone scan was completed, and the patient recovered and was discharged home.

This patient had significant airway obstruction due to deep sedation. Since safe systems and a rescue plan were in place, potential life-threatening complications were avoided.

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The Anesthesia Directed Sedation Service: Models, Protocols, and Challenges

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Children undergo painful or distressing procedures in remote locations where anesthesia providers (anesthesiologists, certified registered nurse anesthetists, anesthesia assistants) are not always readily available. In these situations, sedation models with nonanesthesia care providers are necessary to fill the void that anesthesia services cannot provide. Many procedures do not require general anesthesia (even for the pediatric population), and may be accomplished with varying depths of sedation. Anesthesia, as a specialty, offers a special expertise which can be applied to the development, oversight, and implementation of a sedation service. Anesthesiologists already have knowledge of sedatives, analgesics, and anesthetics and possess the advanced intervention skills necessary to rescue from respiratory and hemodynamic compromise. This specialty has taken an active role in establishing guidelines and standards for the sedation of both adults and children over several decades. In addition, the Institute of Medicine recognizes the field of anesthesia as a model of patient safety: anesthesia associated mortality is currently considered to be as low as 1/200,000 or 300,000 anesthetics administered [1]. Sedation can be considered to be an extension of the specialty: knowledge of the cardiovascular and respiratory physiology, as well as the pharmacology of sedative agents are inherent to this discipline.

Anesthesiologists have contributed a great deal to the development and improvement of the practice of sedation. Historically, one of their most significant contributions was the development of pediatric sedation guidelines in 1983 (published in 1985) [2]. The impetus behind the establishment of these guidelines was a sentinel event, in response to three deaths in a single dental office [3]. These guidelines primarily developed the framework for guidelines which were eventually proposed by the Joint Commission [4].

Some of these initial concepts and recommendations continue to be followed in current practice: The need for informed consent, appropriate fasting before sedation, monitoring of vital signs, and the need for basic life support (BLS) skills. It was also at this stage that the concept of an independent observer for deeply sedated patients was introduced [2]. The only responsibility of this observer was to monitor the patient. The independent observer status would eventually evolve to encompass the administration of medications as well.

Almost 20 years later, the pediatric guidelines were amended in 2002, at which time the term "conscious sedation" [5] was retired. The term "conscious sedation" was viewed a misnomer, an inaccurate representation of the sedated state. In response to the growing demand for sedation standards for non-anesthesiologists, the American Society of Anesthesiology (ASA) first created

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sedation guidelines for nonanesthesiologists in 1996 [6]. Additional guidelines for credentialing nonanesthesiologists were published in 2002 [7] and amended in 2004 [8, 9]. These guidelines introduced capnography as an available, but not required, monitor for moderate sedation. The American Society of Anesthesiologists updated in July, 2011 the Standards for Basic Anesthetic Monitoring [10]. These standards specify that "during moderate or deep sedation the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs and monitoring for the presence of exhaled carbon dioxide unless precluded or invalidated by the nature of the patient, procedure or equipment." Many organizations, including the American Academy of Pediatrics (AAP) and the American Academy of Pediatric Dentistry (AAPD) have incorporated these guidelines into their own practice [11].

While anesthesiologists have created and set the standards for sedation, their availability and ability to meet the growing demand for sedation by being direct caregivers, remains untenable. As the demand for sedation services increase, so does the demand for anesthesia resources in ambulatory centers and satellite areas within and separate from the hospital. In response to the limited number of anesthesia providers, a multispeciality service model has evolved in the United States over the past decade [12]. As a result, many different medical specialties, such as Emergency Medicine, Gastroenterology, Intensive Care Medicine, Hospital Medicine, Pediatrics, and Radiology, established sedation services within their own specialties. In the United States, all these medical subspecialties follow sedation guidelines set by the Joint Commission but morph them to fulfill their unique needs within their own environment. In fact, such organizations, over the years, have gained substantial experience in sedation and considered themselves to be experts in this field. As a result, it is no surprise that anesthesia's involvement in sedation services has been slowly diminishing. In 2005, a survey that was conducted in North America showed that only half of the respondents had indicated that they had a formal sedation service [13]. What was even more surprising was that when only one type of institution-wide service was provided, only 26% of such services involved either pediatric or general anesthesiologists [13].

The apparent diminishing presence of anesthesiologists is initially concerning and seems intuitively counterproductive. In fact, the shortage of providers, particularly anesthesiologists, has been considered to be the most common barrier to the development of a pediatric sedation service [13]. In response to this shortage, many institutions requested that anesthesia departments develop institutional guidelines for provision of sedation by nonanesthesiologists [14]. Initially, anesthesia departments appeared apathetic and disinterested, more focused on meeting the rising demand for anesthesiologists in satellite operating rooms, separate from the operating room. The economics of anesthesia practice relied heavily on revenue generated from the operating room and that area took priority. An editorial written by Wetzel, in Anesthesia and Analgesia in 2006, asked whether it was justifiable to refuse or provide care and, in turn, forbid others from providing such care [15]. He eloquently stated that:

> We cannot eschew responsibility when the solution remains ours.

Development of Protocols

Pediatric anesthesiologists have at their disposal a wide armamentarium of drugs for sedation; many of these medications, such as remifentanil, have a lower margin of safety, but confer some advantages. Table 12.1 is a summary of sedation regimens that have been used by anesthesiologists [16]. Nonanesthesiologists, for the most part, have relied on a more limited array of older and more established medications such as chloral hydrate, pentobarbital, ketamine, and midazolam for many of their procedures [17–23]. There is, however, a willingness and enthusiasm among many of them to expand their expertise in using other sedation medications. While this may mean a better sedation experience for patients, the matter is not without controversy. For example, the use of propofol by nonanesthesiologists engenders such controversy that it has created rifts between specialties [24–27].

Table 12.1 Sedation regimens for children

Drug regimen	Dose/route of administration	Comments (general citations at end of text)
Propofol	100–100 μg/kg/min IV	Ideal agent for nonpainful diagnostic procedures. Only for use by expert airway managers with good back-up systems [62–64]
Pentobarbitol	4–6 mg/kg IV or PO	Long history of effective use in radiology imaging. Emergence can be prolonged [65, 66]
Midazolam	0.5–0.75 mg/kg PO 0.025–0.5 mg/kg IV 0.2 mg/kg intranasal	Track record of safe use both PO and IV. Paradoxical reactions are not infrequent. Intranasal route is so irritating we do not recommend it [67–69]
Chloral hydrate	50–100 mg/kg PO	Still the most popular drug for radiologic sedation in community hospitals. Prolonged sedation and paradoxical reactions are reported. Monitoring required [62, 66, 70]
Etomidate	0.1–0.4 mg/kg IV	Emerging use in emergency medicine for brief painful procedures, although no intrinsic analgesic effect [71–73]
		Post-sedation nausea reported. Little effect on heart rate and blood pressure in most cases.
Methohexital (not readily available at this time)	0.25–0.50 mg/kg IV 20–25 mg/kg rectal	Effective sedation in IV form. Rectal route is not recommended because of high frequency of apnea/desaturation events [74–76]
Propofol with fentanyl	Fentanyl 1–2 μg/kg IV with propofol 50–150 μg/kg IV	Best for deep sedation/anesthesia. Risk of requiring advanced airway management is high [77, 78]
Midazolam with fentanyl	Midozolam 0.020 mg/kg IV Fentanyl 1–2 μg/kg IV	Most common combination for painful procedures in the emergency department. Risk of apnea and hypoxia is significant [79, 80]
Ketamine	3–4 mg/kg IM	Effective sedation and analgesia for painful procedures
	1–2 mg/kg IV	Relatively, common nausea and vomiting after procedure. Laryngospasm reported [81–83]
		Best if combined with an anticholinergic for control of secretions. Combination with midazolam is common, although effectiveness in treating emergence dysphoria is debated
Remifentanil	0.1 μg/kg/min	Emerging use in pediatric sedation, exclusively by anesthesiologists at this point – apnea a significant risk [77, 84–86]
Nitrous oxide	50% in 50% oxygen, up to 70% used by some	Long history of safe use providing moderate sedation for minimally and moderately painful procedures. Care must be taken when used in addition to other sedatives (local anesthetics) where deep sedation can easily result [87–89]

Note: This table shows different medications that are currently used in procedural sedation, with an explanation regarding its use in common practice
Source: From Cravero and Blike [16]. Reprinted with permission from Wolters Kluwer Health

Controversies aside, as the proliferation of different drug regimens continue, particularly among nonanesthesiologists, it may be more prudent to redirect efforts to strengthening the credentialing and training process, rather than restrict certain sedative use. Realistically, it is likely that the term "deep sedation" in children could very well mean periods of general anesthesia. "Conscious sedation" in children is anything but conscious [28]. It seems intuitive then that the skills required to "rescue" a patient from a deep sedation which has progressed to general anesthesia needs careful delineation.

An Anesthesia-Supervised Sedation Team

> Anesthesiologists possess specific expertise in the pharmacology, physiology, and clinical management of patients receiving sedation and analgesia [7].

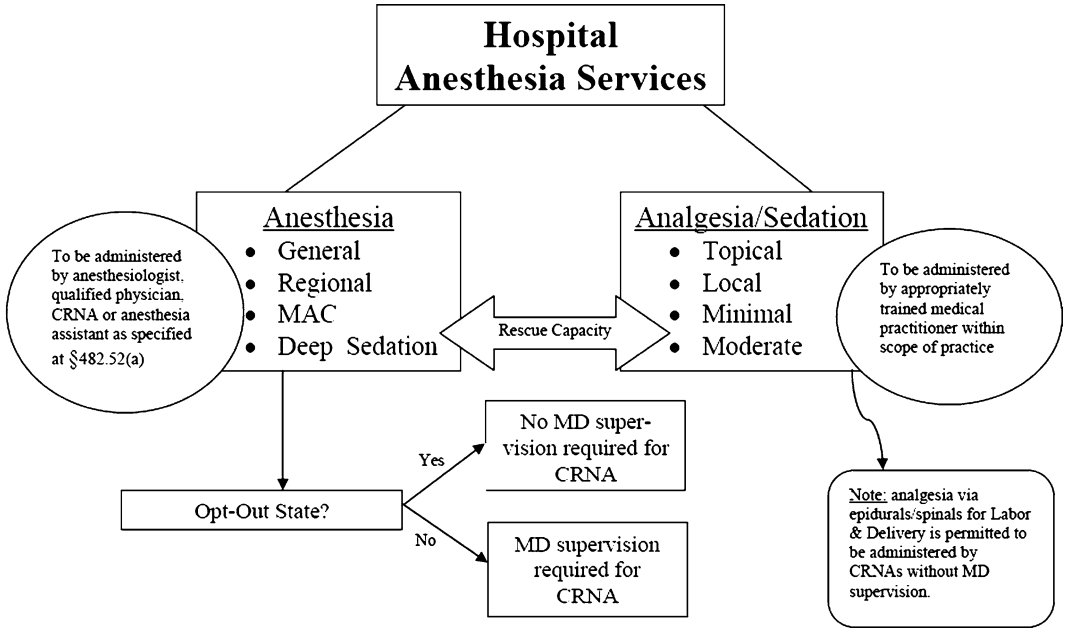

Fig. 12.1 Center for Medicare and Medicaid Services (CMS) revised Hospital Anesthesia Services Interpretive Guidelines – State Operations Manual (SOM) Appendix A [32]. The guidelines presented a proposed organization plan for Hospital Anesthesia Services [32]

Anesthesiologists are trained and proficient in the administration of sedation and have the necessary advanced skills to rescue from any depth of sedation or an inadvertent anesthetic. Providing an anesthesia-delivered sedation service has many challenges. Sedation services are often provided outside the operating room, almost always in areas that are less familiar to the anesthesiologist. The operating room, on the other hand, is definitely within the comfort zone of anesthesia personnel where there is an inherent level of consistency with regard to equipment, space, medications, and availability of help nearby. The delivery of anesthesia in the operating room needs skills in problem recognition and management. These skills may be developed through training that applies a cockpit or pilot response management model designed to promote vigilance and situational awareness [29–31]. Although the pattern of anesthesia delivery in the operating room cannot be precisely duplicated in areas outside the operating room, these training programs can be applied to simulated sedation scenarios outside of the operating room.

Anesthesia-led sedation services consist of different models. In one model, there are anesthesia directed and administered sedation services. All sedation is administered by anesthesiologists or nurse anesthetists. This model has some advantages: anesthesia providers may deliver sedation, monitored anesthesia care (MAC), or general anesthesia, thereby capable of providing all services. The ability to provide all levels of sedation, deep sedation included, is an advantage to an anesthetic care provider model. In February 2010, the Center for Medicare and Medicaid Services (CMS) revised the Hospital Anesthesia Services Interpretive Guidelines – State Operations Manual (SOM) Appendix A [32]. The guidelines presented a proposed organization plan for Hospital Anesthesia Services [32] (see Fig. 12.1). Important amendments included the recognition of deep sedation as a service which falls under MAC. Moderate sedation, in contrast, did not fall under the requirement for anesthesia administration and supervision. MAC according to these guidelines could only be administered by:

1. A qualified anesthesiologist
2. An MD or DO (other than an anesthesiologist)

3. A dentist, oral surgeon, or podiatrist who is qualified to administer anesthesia under State law
4. A CRNA who is supervised by the operating practitioner or by an anesthesiologist who is immediately available if needed

   A CRNA is defined in §410.69(b) as a "…registered nurse who: (1) is licensed as a registered professional nurse by the State in which the nurse practices; (2) meets any licensure requirements the State imposes with respect to non-physician anesthetists; (3) has graduated from a nurse anesthesia educational program that meets the standards of the Council on Accreditation of Nurse Anesthesia Programs, or such other accreditation organization as may be designated by the Secretary; and (4) meets the following criteria: (i) has passed a certification examination of the Council on Certification of Nurse Anesthetists, the Council on Recertification of Nurse Anesthetists, or any other certification organization that may be designated by the Secretary; or (ii) is a graduate of a program described in paragraph (3) of this definition and within 24 months after that graduation meets the requirements of paragraph (4)(i) of this definition" [32].

5. An anesthesiologist's assistant under the supervision of an anesthesiologist who is immediately available if needed

   An anesthesiologist's assistant is defined in §410.69(b) as a "…person who – (1) works under the direction of an anesthesiologist; (2) is in compliance with all applicable requirements of State law, including any licensure requirements the State imposes on nonphysician anesthetists; and (3) is a graduate of a medical school-based anesthesiologist's assistant education program that – (A) is accredited by the Committee on Allied Health Education and Accreditation; and (B) includes approximately two years of specialized basic science and clinical education in anesthesia at a level that builds on a premedical undergraduate science background" [32].

Subsequent to these guidelines, sedation programs which had relied on non-CMS-approved providers to deliver deep sedation, now elected to alter their delivery model. Children's Hospital Boston is one such example. Prior to 2010, the Department of Anesthesia had organized, directed, written protocols for, and directly supervised sedation administered by Registered Nurses [22, 33–37]. The concept of a nurse-led sedation team is not new, and it has been described in hospitals even as early as two decades ago [38, 39]. These nurses were trained in Pediatric Advanced Life Support (PALS) as well as Basic Life Support (BLS). They completed on-line web-based teaching tools that were specific to sedation agents and regimen. Most nurses had critical care or emergency medicine background and had worked in pediatrics. Subsequent to the revised CMS guidelines [32], Children's Hospital Boston altered their sedation model by replacing these registered nurses with nurse anesthetists, a physician, anesthesiologists, anesthesia residents, and anesthesia fellows. All deep sedation now conforms to the February 2010 CMS guidelines.

Nursing administered sedation programs are still prevalent in the United States. Careful physician oversight provides clear boundaries for sedation practice. One such example is the University of Iowa: The University of Iowa continues to maintain a Nurse Sedation Program. In most cases, the level of sedation provided by their sedation nurses is mild to moderate, with a unique model which incorporates propofol administration by registered nurses [40].

Protocols

Protocols developed by anesthesiologists are primarily created for use by nonanesthesiologists. The expertise and knowledge base of anesthesiologists has helped to design-training programs that not only teach sedation related skills, but also evaluate competencies of nonanesthesiologists in all aspects of sedation. The training and teaching can include airway skills, pharmacology of sedation drugs, development of specific drug protocols and collection of Quality Assurance data. In addition to creating such a program, they also have the expertise to monitor sedation practices within an institution. Anesthesiologists have particular expertise and experience in using more than one drug for a sedation event. Their experience in titrating two or more drugs which have potential respiratory and hemodynamic effects has been very useful in developing protocols. We shall describe a few of the drug protocols developed primarily by anesthesiologists.

Ketamine

Ketamine has been used as an adjunct analgesic and hypnotic medication for many procedures. The analgesic effects of ketamine are present in plasma concentrations that are significantly lower than those producing hypnosis (0.2 vs. 1.5–2.5 μg/mL) [41].

A sedation protocol using intravenous (IV) ketamine for radiological procedures is being successfully used by radiology nurses at Children's Hospital Boston. During the development of the protocol, ketamine doses and administration methods were studied and refined according to patient outcomes [21]. The outcomes of sedated patients relies on an adequate screening process whereby patients were selected based on established criteria for nurse sedation, without any contraindications to ketamine use (see Fig. 12.2) [21]. There were many procedures that took less than 10 min duration. An intramuscular ketamine protocol was developed for children without IV access who required sedation for insertion of a peripherally inserted central catheter (PICC) (see Fig. 12.3) [21]. The IV ketamine protocol was also developed to require the use of an infusion of ketamine for procedures longer than 10 min (see Fig. 12.4) [21]. The ability of radiologists to use this protocol independently for a select group of patients has allowed increased flexibility in scheduling of these cases, as well as provided an alternative to general anesthesia. However, the authors do recommend that an anesthesiologist be immediately available for airway emergencies [21].

CONTRAINDICATIONS TO USE OF KETAMINE

1. Active pulmonary infection or disease
2. Know or potential (ie, risk of) airway compromise
3. Pulmonary hypertension
4. Age of 3 months or younger
5. History of apnea, obstructive sleep apnea
6. Craniofacial defect that would make mast ventilation difficult
7. Complex caridiac disease
8. Intracranial hypertension (ie, central nervous system mass lesions, hydrocephalus, head injuries associated with increased intracranial pressure); IF THERE IS ANY DOUBT, PLEASE HAVE RADIOLOGIST CONSULT ORDERING PHYSICIAN TO DETERMINE WHETHER THERE IS INCREASED INTRACRANIAL PRESSURE RISK
9. Acute globe injury
10. Prior adverse reactions to ketamine
11. History of bipolar disease or schizophrenia
12. Head injury associated with loss of consciousness, altered mental status, or emesis
13. Any child in whom there is a question of increased intracranial pressure
14. Child with a potential ventriculoperitoneal shunt malfunction
15. Patient or parent refusal
16. Increased intraocular pressure

Fig. 12.2 This figure outlines the contraindications on the use of ketamine in the protocol used by Children's Hospital Boston for procedural sedation [21]

Ketamine has also been used as an adjunct with propofol to provide adequate conditions for performing procedures. Though ketamine has analgesic effects, it is believed that using it as an adjunct would allow lower doses of propofol to achieve the appropriate sedation level. A protocol created for auditory testing (ABR), created by Akin et al., showed that addition of ketamine of 0.5 mg/kg to an initial dose of 1.5 mg/kg of propofol in kids aged 1–13 years decreased the need for additional boluses of propofol at half the starting dose [42]. Quite often, ketamine is used in combination with propofol for procedures associated with pain. A study performed by Tosun et al., showed that the combination of propofol and ketamine was very effective for pediatric burn dressing changes [43]. In fact, it was found to be superior to using a propofol-fentanyl combination since more restlessness was found in the propofol-fentanyl group. In this study, the propofol-ketamine group received 1 mg/kg ketamine and 1.2 mg/kg propofol, and the propofol-fentanyl group received 1 μg/kg of fentanyl and 1.2 mg/kg of propofol for sedation induction. Additional propofol (0.5–1 mg/kg) was administered, as necessary, for discomfort. A very similar study using the same drug combinations and doses, in which a ketamine-propofol combination was compared to ketamine and fentanyl [44], was performed for upper endoscopic procedures. The propofol-ketamine combination provided better tolerance of the endoscope insertion and better hemodynamic stability. However, there were more side effects with ketamine such as dizziness, diplopia, and vomiting. Restlessness during endoscopy was observed more often in the propofol-fentanyl group than in the propofol-ketamine group.

INTRAMUSCULAR KETAMINE FOR PROCEDURES (ONLY FOR PICC LINE PROCEDURE OR AFTER ≥ 3 FAILED IV ATTEMPTS(FILL IN BELOW)

☐ **<5 YEARS OF AGE**

Glycopyrrolate 0.005 mg/kg x_____kg = _____ mg IM x1

Ketamine 4 mg/kg x _____kg= _____ mg (max 200 mg/dose)Mx1

Mix together in one syringe and give IM x 1 in deltoid. Use concentrated form of ketamine (100 mg/mL).

May repeat Ketamine 2 mg/kg x _____kg = _____mg (max 100 mg/dose) IM x 1 after 45 minutes.

☐ **≥5 YEARS OF AGE**

Glycopyrrolate 0.005 mg/kg x_____kg = _____ mg IM x1

Midazolam 0.1 mg/kg x _____kg = _____ mg (max 3 mg/dose) IM x 1

Ketamine 1 mg/kg x _____kg = _____ mg (max 200 mg/dose) IM x 1

Mix together in one syringe and give IM x 1 in deltoid. Use concentrated form of ketamine (100 mg/mL).

May repeat Ketamine 2 mg/kg x _____ kg = _____ mg (max 100 mg/dose) IM x 1 after 45 minutes.

Fig. 12.3 This protocol is primarily for ketamine use when intravenous access is difficult or not attainable. The age groups are divided into children less than 5 years and children greater than 5 years [21]

INTRAVENOUS KETAMINE FOR PROCEDURES <10 MINUTES (FILL IN BELOW)

☐ **<5 YEARS OF AGE**

Glycopyrrolate 0.005 mg/kg x _____ kg = _____mg IV x1

Ketamine 1 mg/kg x _____kg = _____ mg (max 70 mg/dose) IV x1.
May repeat x 1 dose if patient still responsive to nailbed pressure after 1 minute.

☐ **≥5 YEARS OF AGE**

Glycopyrrolate 0.005 mg/kg x _____ kg = _____mg IV x1

Midazolam 0.1 mg/kg x _____kg = _____mg (max 07 mg/dose) IV x1.

Ketamine 1 mg/kg x _____kg = _____mg (max 07 mg/dose) IV x1.
May repeat x1 dose if patient still responsive to nailbed pressure after 1 minute.

INTRAVENOUS KETAMINE FOR PROCEDURES >10 MINUTES (FILL IN BELOW)

☐ **<5 YEARS OF AGE**

Glycopyrrolate 0.005 mg/kg x _____ kg = _____mg IV x1

Ketamine 1 mg/kg x _____kg = _____ mg (max 70 mg/dose) IV x1.
May repeat x 1 dose if patient still responsive to nailbed pressure after 1 minute.

Ketamine 100 mcg/kg/minx _____kg = _____mcg/min IV drip to be iniated immediately after ketamine bolus above. Dilute ketamine to 10 mg/mL for continuous infusion. Assess patient Q10min for response to nailbed pressure. Titrate ketamine drip as necessary between 50 -125 mcg/kg/min.

Notify anesthesia if ketamine continuous infusion exceeds 60 minutes.

☐ **≥5 YEARS OF AGE**

Glycopyrrolate 0.005 mg/kg x _____ kg = _____mg IV x1

Midazolam 0.1 mg/kg x _____kg = _____mg (max 07 mg/dose) IV x1.
May repeat x 1 dose after 60 to 80 minutes if sedation still needed.

Ketamine 1 mg/kg x _____kg = _____ mg (max 70 mg/dose) IV x1.
May repeat x 1 dose if patient still responsive to nailbed pressure after 1 minute.

Ketamine 100 mcg/kg/minx _____kg = _____mcg/min IV drip to be iniated immediately after ketamine bolus above. Dilute ketamine to 10 mg/mL for continuous infusion. Assess patient Q10min for response to nailbed pressure. Titrate ketamine drip as necessary between 50 -125 mcg/kg/min.

Notify anesthesia if ketamine continuous infusion exceeds 60 minutes.

Fig. 12.4 Ketamine protocol for those who have adequate intravenous access. The protocol is divided into procedures less than 10 min and procedures greater than 10 min. Within these subdivisions, the protocol outlines doses for children less than 5 years and children greater than 5 years [21]

Another study compared a combination of dexmedetomidine and ketamine to a combination of ketamine and propofol for cardiac catheterization. The dexmedetomidine group had increased recovery time and required more ketamine than the propofol-ketamine combination [45]. In this study, one group received a dexmedetomidine and ketamine combination (1 μg/kg over 10 min and 1 mg/kg respectively) followed by dexmedetomidine infusion of 0.7 μg/kg/h and ketamine at 1 mg/kg/h.

Pentobarbital

The superiority of pentobarbital over choral hydrate was evident in a study of over 1,400 patients where pentobarbital was associated with a decreased incidence of adverse events [19]. In this study, the dose of oral pentobarbital used was 4 mg/kg that may be supplemented at aliquots of 2 mg/kg every 30 min to a maximum dose of 8 mg/kg [19].

Although the relative safety of the drug has been demonstrated, the drug has a relatively long half-life ranging between 15 and 48 h [46].

Dexmedetomidine

Dexmedetomidine is a highly selective α2 adrenoceptor agonist that has sedative and analgesic effects [47]. It is unique in that it is FDA approved as a sedative and has been shown to induce non-REM natural sleep [48, 49]. A sedation protocol using dexmedetomidine was developed at Children's Hospital Boston for Computed Tomography (CT) imaging. Although dexmedetomidine does not have any contraindications, their protocol advocated relative contraindications which are based predominantly on medical conditions [33] (see Table 12.2).

Patients would receive an initial loading dose of 2 μg/kg IV dexmedetomidine over a 10-min period, with appropriate monitoring. Using the Ramsay Sedation Scoring System, the child would receive an additional bolus of 2 μg/kg IV over 10 min to reach a Ramsay Sedation Score (RSS) of 4. Once the child achieves this level of sedation, the sedation is maintained with an infusion dose of 1 μg/kg/h until the procedure is finished. The patient is then transported to a recovery area until discharge criteria based on a modified Aldrete score is achieved [33]. This protocol has a low incidence of adverse events. The success of this protocol led to an expanded use of the drug in Magnetic Resonance Imaging (MRI), but the doses were increased to a 3 μg/kg bolus over 10 min which could be repeated if the level of sedation was not achieved. This was followed by an infusion rate of 2 μg/kg/h for the duration of the MRI [34]. This high dose regimen was highly effective for completion of almost all MRIs. While use of high dose dexmedetomidine is associated with decreases in heart rate and blood

Table 12.2 Contraindications on the use of dexmedetomidine as outlined in the Children's Hospital Boston guidelines

Dexmedetomidine
Active, uncontrolled gastroesophageal reflux
Active, uncontrolled vomiting
Current (or within the past 3 months) history of apnea requiring an apnea monitor
Active, current respiratory issues that are different from the baseline status (pneumonia, exacerbation of asthma, bronchiolitis, respiratory synctitial virus)
Unstable cardiac status (life-threatening arrhythmias, abnormal cardiac anatomy, significant cardiac dysfunction)
Craniofacial anomaly, which could make it difficult to effectively establish a mask airway for positive pressure ventilation if needed
Current use of digoxin, beta blockers, or calcium channel blockers
Moya Moya disease
Nononset stroke

Source: From Mason et al. [33]. Reprinted with permission of Wolters Kluwer Health

pressure outside the established "awake" normal values, this deviation is generally within 20% and is not associated with adverse sequelae.

Dexmedetomidine sedation has probably revolutionized sedation for imaging studies primarily for its safety and recovery profile [34, 37, 50]. There has been a case report whereby a 21-month-old female received 60 times the intended dose without any harm to the patient [51]. When administered as a sedative by non-anesthesiologists, dexmedetomidine may be supervised by an anesthesiologist who is not in continuous attendance but who may in fact be directing multiple sedation events in contiguous locations.

Propofol

Propofol, as a sedation drug, is perhaps the most controversial sedative agent currently used. It is not Food and Drug Administration (FDA) approved as a sedative, but rather is considered an anesthetic agent [52]. Its controversy lies in its respiratory depressant and hemodynamic side effects. Therefore, it requires careful titration and monitoring during its use. The package insert specifies that its use be restricted to those who are able to administer general anesthesia. In April 2004, the American Association of Nurse Anesthetists and American Society of Anesthesia made a joint statement on the need for restricting the use of propofol [53]:

> Whenever propofol is used for sedation/anesthesia, it should be administered only by persons trained in the administration of general anesthesia, who are not simultaneously involved in these surgical or diagnostic procedures. This restriction is concordant with specific language in the propofol package insert, and failure to follow these recommendations could put patients at increased risk of significant injury or death.

This statement has created much controversy among many physicians, such as intensivists, emergency room physicians, gastroenterologists and pediatricians who indicate that this position statement significantly restricts the use of this drug. The American College of Gastroenterologists filed a petition to ask the FDA to remove the restriction as written on the propofol label [54]. However, the FDA denied the request. They concluded that:

> For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectible Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure [54].

While these concerns over the safety of propofol for use by nonanesthesiologists continue, it appears that the controversies surrounding use of propofol by nonanesthesiologists may be unfounded. A review of prospectively collected data on approximately 49,000 propofol sedations by both anesthesiologists and nonanesthesiologists showed a low incidence of adverse outcomes [55]. "Nonanesthesiologists" included advanced nurse practitioners, pediatric nurses, physician's assistants, emergency physicians, pediatric intensivists, and radiologists. At least 48 and 36% of the sedations were performed by intensivists and emergency physicians, respectively. It was, however, interesting to note that anesthesia-related services using propofol were associated with fewer adverse events than nonanesthesiology providers [55]. A report of 25,433 propofol sedations to children by emergency medicine physicians, most for radiological imaging studies, demonstrated a 2.28% incidence of serious adverse events [56].

Nonetheless, the proliferation of use of propofol by anesthesiologists (and nonanesthesiologists alike) shows that it is a remarkably versatile drug to use for sedation. There are several advantages in the use of propofol: a rapid onset of action, it is easily titrable, and it allows a rapid recovery. Despite its lack of a reversal agent, propofol's duration of action is short. In addition, it has antiemetic properties. However, it has serious cardiac and respiratory morbidity and mortality risks and should only be used with appropriate training and monitoring. Sedation can be performed with this drug without compromising respiratory drive by appropriately titrating the agent. However, since it has no analgesic effects, there may be a need for appropriate concomitant analgesic agents. The combination of propofol-ketamine or propofol-fentanyl has been described previously and can be safe and effective [43].

Nursing Delivered Propofol

Nursing Delivered propofol has been controversial because its use needs to be restricted according to governing bodies such as the ASA and the Food and Drug Administration; both of which have issued statements that it should only be used by professionals trained in performing general anesthesia [53, 57]. The 2010 CMS amendment to the Hospital Anesthesia Services Interpretive Guidelines reflected these underlying concerns and was subsequently revised again [32]. These CMS guidelines were again revised in January 2011 in the PUB 100-07 State Operations Provider Certification which revises Appendix A for various provisions of 42 CFR 482-52 concerning anesthesia services [58]. These revisions were made in response to feedback from practitioners. Important changes in these guidelines stem from the CMS acknowledgement that the individual hospitals may establish their own policies and procedures with respect to the qualifications of analgesia providers and the clinical situations which distinguish anesthesia from analgesia. The policies must follow nationally recognized guidelines and can include guidelines of one or more specialty societies.

The University of Iowa has developed and implemented a unique propofol-delivered sedation program under the direction of the Department of Anesthesia. This program, initiated in 2008, is an example of a carefully designed and supervised model of propofol administration by registered nurses (RN). The history of the program is important and will be detailed below. The chronological retelling of the history illustrates not only the politics, but also the evolution of the program. The original premise of our consideration for use of propofol was that these RNs would always be carefully supervised by an anesthesiologist, and they would be trained to possess the airway skills necessary for deep sedation. The training program already emphasized the need for advanced airway training, which included the use of rescue devices such as a laryngeal mask airway. We also took into account the skills of the nurses, the type of procedures, the duration of the procedures, and the location of the procedures as a preamble to initiation of propofol sedation. At the inception of the program, propofol was not introduced and would not be considered until the nurses acquired experience with already established sedation protocols using pentobarbital, ketamine, midazolam, and fentanyl; most of which were protocols developed at Children's Hospital Boston [20, 21]. In the meanwhile, the Iowa Board of Nursing, proactive to rumors of possible propofol delivery by RNs to nonintubated patients, issued a statement: propofol could not be administered by nurses in the state of Iowa except on intubated patients in the Intensive Care Unit (ICU) and similar settings. Nurse anesthetists had already voted against RN administered propofol and the Board followed with a position paper after voting "to find that it is not within the scope of practice of the registered nurse to administer Propofol (Diprivan) during operative, invasive and diagnostic procedures in any type of health care setting effective December 1, 2007" [59]. Plans and education for RN-administered propofol at University of Iowa were subsequently aborted.

Our nurses, in the interim, continued to acquire sedation experience with drugs such as ketamine, pentobarbital, fentanyl and midazolam, as well as dexmedetomidine. The Pediatric Gastro-Intestinal Services team preferred propofol over ketamine, fentanyl, and versed combinations because there was a shorter recovery time and lower incidence of nausea and vomiting (despite pretreatment with anti-emetics). Physicians (including representation from our Department of Anesthesia), advanced nurse practitioners, and registered nurses returned to the Iowa Board of Nursing in 2008 and made a strong case for the negative impact on patient care caused by propofol restrictions [60]. The Iowa Board of Nursing subsequently rescinded the rule of restriction for the use of propofol by RNs [60].

Immediately after the rule was rescinded in September 2008, we initiated training of our RNs on the use of propofol for sedation purposes. The nurses already understood the use of End Tidal CO_2 monitoring in addition to other standard monitoring modalities. They also understood the importance of a defined, structured, propofol protocol which was founded on published reports of successful drug doses and combinations [41, 61].

Children < 10 years of age: Propofol-Ketamine Infusion

- Midazolam: 0.1 mg/kg IV - (Max 2 mg) Use as needed for anxiety
- Glycopyrrolate: 0.005 mg/kg IV (Max 0.2 mg) use for all Propofol procedures
- Initial P/K bolus: 0.5 mg/kg/0.05 mg/kg IV - (may be repeated Q30 seconds till Riker 3)
- Infusion P/K: 100-125 mcg/kg/min (use on procedures >20minutes)
- AS needed: Bolus Propofol 0.5mg/kg IV prn Q30 seconds until Riker 3

(HOLD Boluses and/or infusion if RR less than 20% of baseline or BP MAP less than 20% of Baseline)

Children > 10 years of age: Propofol Infusion ONLY

- Midazolam: 1-2 mg IV (Max 2mg) Use as needed for anxiety
- Initial Propofol bolus: 0.5 mg/kg IV – (May be repeated Q30 seconds until Riker 3)
- Infusion Propofol: 150 mcg/kg/min (use on procedures >20minutes)
- As needed: Bolus Propofol 0.5mg/kg IV prn Q30 seconds until Riker 3

(Hold Boluses and/or infusion if RR less than 20% of baseline or BP MAP less than 20% of Baseline)

FLUID BOLUS: 10-20 ml/kg IV for all children (discuss with Anesthesiologist for children with congenital heart disease before bolus is administered)

P:K= 10:1 :Preparation of ketamine propofol mixture:

50ml Propofol vial = 500 mg of 10mg/ml: TAKE 50ml of propofol

5ml Ketamine vial = 500mg of 100mg/ml: TAKE 0.5ml of ketamine

P-K total volume = 50 ml + 0.5 ml = 50.5 ml →

P-conc. = 9.9mg/ml in mixture of propofol and ketamine

K-conc = 0.99 mg/ml in mixture of propofol and ketamine

Fig. 12.5 University of Iowa: Nonanesthesiologist delivered propofol protocol

Children <10 years of age would receive a drug combination of propofol and ketamine in the ratio 10:1 up to a maximum dose of 125 μg/kg/min. The ketamine was intended to provide some analgesic and propofol sparing effect. The protocol evolved after review of Outcome and Quality Assurance data. Ketamine was not an adjunct to propofol for procedures in children >10 years of age, for fear of hallucinations, nausea, and vomiting in that age group. Initially, the time interval between boluses was at 1 min intervals and was slowly reduced to 15 seconds after the nurses gained experience.

Propofol is now being administered using established protocols at the University of Iowa for endoscopies, bronchoscopies, and radiological imaging studies. Every patient is assessed and consented by the anesthesiologist. (The sedation nurse independently assesses the patient first and also discusses the sedation process.) Each day an anesthesiologist is assigned to supervise sedation and has no concomitant operating room obligations. The anesthesiologist is usually present during the initial phase of propofol sedation and will remain immediately available for the rest of the case. After the procedure is complete, the propofol infusion is discontinued and the patient is transported on monitors (including end tidal CO_2) to the recovery room. The recovery nurses are allowed to discharge the patient based on preestablished discharge criteria. The anesthesiologist will see the patient before discharge if there were any issues during sedation or if a concern was brought up by a recovery nurse.

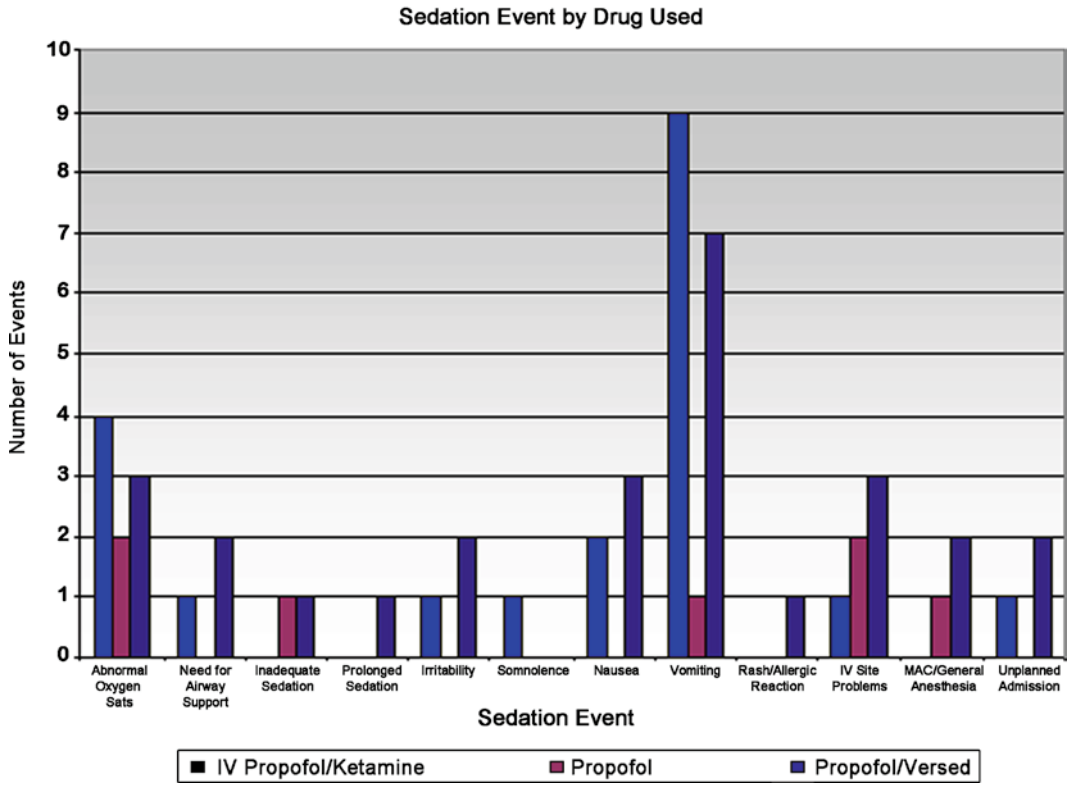

Fig. 12.6 This graph outlines the sedation related events associated with the use of propofol alone and in combination with ketamine and versed. The events shown include side effects of drugs such as nausea and vomiting, airway associated problems such as abnormal oxygen saturations, quality of sedation such as inadequate sedation, IV site problems, and adverse events such as unplanned admissions. (University of Iowa Propofol Sedation Program. Incidence of Adverse Events $n = 1{,}500+$ sedations.) Created by Joss J. Thomas, MBBS, MPH; University of Iowa Hospitals and Clinics, Iowa City, IA

The anesthesiologist can supervise multiple sedations in contiguous locations at the same time. However, the anesthesiologist can also restrict the volume to one sedation at a time, if it is deemed necessary for safety. For example, if a medically challenging patient needs closer supervision and monitoring, the schedule is modified to enable the anesthesiologist to only supervise this pre-sedation. A propofol template order set has been created on the electronic medical record system and these orders are signed by an anesthesiologist. The sedation nurses retrieve the propofol from the the operating room pharmacy. The order set is exclusively used by the sedation team (see Fig. 12.5).

Since October 2008, there have been over 1,500 propofol sedations. Initial unpublished data indicates a low incidence of adverse events (see Fig. 12.6). There were three unanticipated hospital admissions. The first admission was a 6-year-old male who had multiple oxygen desaturations to the high 80's during an endoscopy and was admitted to the hospital for observation. The second case was a 4-month-old male who suffered protracted coughing episodes during G-J tube placement. He was transferred to the pediatric intensive care unit (PICU) intubated, and subsequently extubated with no further issues. Finally, a 35-month-old male desaturated to the low 80's during upper endoscopy and required positive pressure bag-mask assisted ventilation. He was admitted to PICU and was intubated. Follow-up revealed that this child had an unrecognized upper airway condition which, had it been noted on the prescreening evaluation, would have contraindicated the sedation. This experience reiterates the

importance of careful screening, protocols, and guidance as anesthesia develops sedation programs for nonanesthesiologists.

Conclusion

An anesthesiology-directed sedation team can provide a safe and efficient sedation service. While it would be ideal that anesthesia personnel are always available to provide such a service, the reality is that the priority for anesthesia resources remains with the operating room. Very few centers have adopted a model such as an anesthesia-supervised nurse sedation team and, unfortunately, anesthesia's presence outside the operating room as a sedation provider remains limited. In response to this shortcoming, various other specialties, such as gastroenterologists, emergency room physicians, pediatricians and radiologists, have taken up the responsibility to provide this service. It is important to recognize that the Department of Anesthesia still has to play an integral role in monitoring sedation practices in an institution and developing the standards of training, monitoring and credentialing nonanesthesiologists to provide sedation services. The Centers for Medicare and Medicaid (CMS) recently revised the guidelines regarding delivery of anesthesia services [32]. For the first time, deep sedation was included as part of anesthesia services. CMS proposed that there be a consolidation of anesthesia services:

> All services along the continuum of anesthesia services provided in a hospital must be organized under a single Anesthesia Service [32].

Apropos to these guidelines, the Department of Anesthesia may need to play a more active role in the management and oversight of sedation services throughout the institution.

Case Studies

Case 1: Bronchoscopy with Sedation

A 5-month-old female weighing 7 kg (52% of growth percentile based on length-for-age) is being evaluated by bronchoscopy for persistent cough and expiratory wheeze. The child was otherwise healthy, with normal baseline vitals and saturations of 99% on room air. She had coarse expiratory crackles on auscultation, but other systems were normal. The pulmonologist wanted to perform a dynamic airway evaluation as well as obtain a broncheoalveolar sample.

***Considerations*:** The very nature of patients who require bronchoscopy makes them more susceptible to airway- and respiratory-based problems. These patients have a respiratory status that is already compromised secondary to an airway problem, such as laryngomalacia. They are likely to have sustained an infection such as unresolved pneumonia or a persistent reactive airway. It is advised not to sedate a patient until 4–6 weeks after a pneumonia or pulmonary infection. However, such recommendations do not apply to patients who require a bronchoscopic evaluation. Therefore, these patients are at an increased risk of respiratory decompensation during sedation.

The level of sedation that is required changes with the indication for bronchoscopy. When a dynamic airway evaluation is required to assess for airway related problems, especially laryngomalacia, tracheomalacia, and bronchomalacia, a moderate level of sedation would allow the collapse of airways to be better visualized during vigorous work of breathing. Our pulmonologists have indicated that such potential diagnoses of airway problems can be missed when sedation is deeper than intended. On the other hand, a deeper level of sedation is ideal to attain bronchioalveolar lavage (BAL) samples. In some patients, a moderate level of sedation, followed by a deeper level of sedation, are both required as the pulmonologist performs a dynamic airway evaluation and subsequently obtains a BAL sample.

It has been our experience that changing the level of sedation can be a potential challenge during these procedures. Propofol allows rapid changes in depths of sedation with careful titration of the medication.

***The Sedation*:** The patient was sedated with propofol, at 0.5 mg/kg boluses, after an initial dose of glycopyrrolate at 0.005 mg/kg and midazolam at 0.1 mg/kg. Local topical lidocaine was applied by the pulmonologist based on a weight-based protocol.

During the procedure, the pulmonologist performed an airway evaluation with the bronchoscope via the nares. With moderate sedation, they noticed no laryngeal or tracheal malacia, but it was difficult to note if there was malacia in the right middle lobe. Mucous secretions were prominent in the right lobe and particularly in the right middle lobe. The patient was then deeply sedated during the BAL procedure with additional propofol. However, the patient required bag-mask ventilation for ten breaths after a bolus of propofol elicited a brief oxygen desaturation to the 70's during the BAL. The patient required CPAP for approximately 10 min after the procedure (for persistent desaturations to the 80s without CPAP). This was likely due to possible atelectasis post-procedure and perhaps also related to sedation. The patient recovered uneventfully with saturations of 97–100% on room air within 4 h. An aggregate total of 26 mg of propofol was administered to the child. The child was discharged with a working diagnosis of inflammatory airway disease of unknown etiology.

Case 2

A 4-year-old male with a left suprarenal neuroblastoma, which was metastatic to multiple locations including the right maxilla and orbit, requires a surveillance scan under sedation. He had undergone multiple rounds of chemotherapy and resection of his left adrenal gland, and had subsequently undergone two stem-cell transplants and chemotherapy with thiotepa and cyclophosphamide. Radiation therapy was complicated by renal insufficiency. We were consulted to help with sedation for a surveillance scan, which included a chest/abdomen/pelvis CT and a whole body nuclear bone scan. The child has had multiple imaging studies done before, and it was necessary to use a nasogastric tube for oral contrast since he refused to drink any medication or fluids during earlier imaging procedures at the hospital.

***Considerations*:** He would need to have an intravenous line placed for intravenous fluid hydration and intravenous contrast prior to the scan. A nasogastric (NG) tube would need to be placed for oral contrast. The additional comorbidity of renal insufficiency necessitated using a radio contrast-induced nephropathy prevention protocol that included appropriate hydration with fluids and bicarbonate intravenous drip for renal protection prior to, and immediately after, the intravenous contrast load required for chest CT imaging.

Further preparation for the nuclear scan indicated that there would be at least a 2 hour waiting time, during which the child need not be sedated. During this period he would get adequate hydration and a bicarbonate-based infusion.

***The Sedation*:** The child and parents were habituated to receiving intramuscular chemotherapy and requested this route of administration for sedation. A combination of 0.1 and 5 mg/kg of versed and ketamine respectively were administered intramuscularly. The child was adequately sedated for placement of the NG tube, intravenous line, and oral contrast. The child was allowed to wake up after oral contrast was given. After about 2 hours, the child was re-sedated using propofol infusion at 125–150 μg/kg/min, and the CT scan and bone scan were completed

without incident. While an intramuscular injection of sedation medications is not routine for patients who require oral contrast imaging studies, it was necessary to tailor a regimen that would facilitate the process of attaining good imaging studies while keeping the child comfortable. In such situations, eliciting the help of parents to assist with the administration of medications is sometimes necessary. The option of general anesthesia has been proposed as an alternative to the sedation, but since this procedure was likely to be repeated every 3–6 months, the parents preferred sedation.

Case 3

Three-year-old female with a past medical history positive for tracheomalacia, follicular bronchitis, subglottic stenosis, and esophageal reflux, needed a pH impedance probe placed by the pediatric gastroenterology team under sedation.

Patient was diagnosed with esophageal reflux since she was 3 weeks old. She had a persistent cough. She developed croup twice, and was diagnosed with laryngomalacia and follicular bronchitis.

***Considerations*:** The anesthesia team was concerned with her respiratory status and tracheal stenosis. She had been easily intubated with a size 4 ETT tube 2 months prior. The concern about aspiration risk was discussed, but the gastroenterology (GI) service following her indicated that this was chronic micro-aspiration. The patient's mother indicated that the child had no vomiting episodes. The placement of an impedance probe was a very short procedure routinely done under sedation. However, the anesthesiologist was concerned about the respiratory status since the patient probably had a low reserve (though her saturations were 99% on room air).

***The Sedation*:** After having discussed the concerns with the pediatric GI team, it was agreed to proceed with sedation. The anesthesiologist was at the bedside throughout. The patient was sedated with a propofol-ketamine mixture 10:1 ratio at 125 μg/kg/min with boluses at 0.5 mg/kg every 30 seconds as necessary. Using an Olympus Q180 video endoscope, the patient's esophagus was intubated without difficulty. The entire length of the esophagus was normal, without ulcerations, edema, erythema, or furrowing. The lower esophageal sphincter was normal. Upon entering the stomach, normal gastric mucosa was seen without erythema, ulcerations, or other lesions. The pylorus was normal and was easily traversed to enter the duodenum where, again, normal mucosa was visualized, with normal villi and no ulcerations or other abnormalities.

Following attempted placement of the pH impedance probe, the patient had a brief desaturation episode to the 30's after coughing for 30 seconds. She was mask ventilated after removal of the scope and probe. Her oxygen saturations responded immediately from low 30's to high 90's. It is likely that the impedance probe may have entered the airway. Once the oxygen saturations stabilized, the impedance probe was replaced without difficulty. The rest of her hospital stay was uneventful.

***Summary Thoughts*:** This case would probably have benefited from general anesthesia with an endotracheal tube to protect the airway. Though the pediatric GI team routinely places these pH impedance probes under sedation, the probe can inadvertently enter the airway. This case highlighted different viewpoints of risk vs. benefit between specialties on issues such as aspiration risk. The consideration of an aspiration risk vs. potential edema and further comprise of an already stenosed airway secondary to intubation, persuaded the anesthesiologist to

maintain spontaneous ventilation and avoid endotracheal intubation. However, the probability of the impedance probe entering the airway, even in good hands was probably not recognized as a concern. The pediatric GI team indicated that it is very rare for them to enter the airway because it is done under direct visualization with the scope.

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Sedation in the Intensive Care Unit: Challenges, Outcomes, and Future Strategies

13

Joseph D. Tobias

Introduction

On a daily basis, infants and children in the Pediatric Intensive Care Unit (PICU) require sedation and analgesia during painful and invasive procedures. Regardless of the patient's age, underlying medical condition or comorbidities, admission to and subsequent care in the PICU can be a frightening and painful experience. As in other locations, procedures may be brief (burn dressing changes, placement of central venous or arterial cannulae), and require only a short period of analgesia, anxiolysis, or immobility. However, the PICU is often different from other locations, as the need for procedural sedation may last days or even weeks as children may require prolonged sedation to overcome the pain and anxiety associated with the presence of an endotracheal tube (ETT) and the requirement for ongoing mechanical ventilation. The pain and anxiety may be further magnified by various psychological factors including periodic separation from parents, disruption of the day–night cycle, unfamiliar people, the noise of imposing machines and monitoring devices, fear of death, and loss of self-control can lead to emotional distress, anxiety, and sleeplessness. In a recent prospective cohort study of adult patients, Mendelsohn et al. reported that 26.3% of their cohort remembered mechanical ventilation and approximately 25% would have chosen not to receive mechanical ventilation had it been any more painful [1].

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Pediatric ICU Sedation

Preprocedure Preparation and Patient Evaluation

Before the administration of pharmacologic agents for the control of procedure-related pain and anxiety, there should be an evaluation of the patient and preparation of the environment (Table 13.1). The Pediatric ICU patient is somewhat different in that treatable and potentially life-threatening causes of agitation such as hypoxemia, hypercarbia, cerebral hypoperfusion, necrotic bowel, or a compartment syndrome must be excluded before instituting sedation or escalating doses. The injudicious use of sedative/analgesic agents without ongoing patient examination and monitoring may be deleterious. Alternatively, such concerns are less of an issue for a patient who is undergoing a brief invasive or noninvasive procedure.

The basic components of the presedation assessment are outlined in Table 13.2. This assessment includes the performance of a focused history and physical examination. The history

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Table 13.1 Preparation for procedural sedation in the pediatric ICU

Rule out treatable causes of agitation
Hypoxia and hypercarbia
Cerebral hypoperfusion
Bladder distention
Surgical lesion – necrotic bowel or compartment syndrome
Perform a presedation evaluation of the patient. This evaluation is similar to that performed prior to any surgical procedure performed in the operating room
Identify the etiology of the pain or agitation to guide the appropriate selection of the agent or agents as well as the need to provide sedation/anxiolysis/amnesia, analgesia or both
Monitor patient according to the standards outlined by the American Academy of Pediatrics for procedural sedation and analgesia [2]
Titrate the initial bolus dose of the medication and subsequent infusion rates based on the patient's clinical response with the use of formalized sedation/pain scales
Observe for adverse physiologic effects including the development of physical tolerance which necessitates increasing the dose of the agent used or switching to another agent that acts through a different receptor system

Table 13.2 The preprocedure or presedation assessment

Patient's name, age weight, and gender
Past medical history
Acute medical or surgical problems
Comorbid medical conditions
Previous sedation or anesthetic history including problems
Allergies
Current medications
Family history of anesthetic complications
Dietary history (nil per os status)
Pregnancy history
Physical examination
Baseline vital signs including room air oxygen saturation if feasible
Airway examination with Mallampati grading system
Focused cardiac and respiratory examination
Current vascular access and infusion (to select site for medication administration)
Laboratory evaluation as appropriate
Summary
American Society of Anesthesiologists status (ASA I–V)
Sedation and recovery plan
Risks discussed and informed consent obtained from patients

should focus on the child's current state of health as it relates to the reason for the procedure, the past medical history to identify significant comorbidities, as well as acute events which led to the PICU admission. Since the primary risks associated with sedation include adverse respiratory events (apnea, hypoxemia, hypercarbia, and upper airway obstruction) or cardiovascular events (hypotension, bradycardia, arrhythmias), the focus of the presedation evaluation and physical examination is placed on these systems or areas. Although many patients may already have an ETT in place, the assessment of the upper airway should still be performed in the event that the ETT become dislodged at some time such as during positioning for the procedure or patient transport. Upon completion of the history and physical examination, an ASA (American Association of Anesthesiologist) classification may be assigned and the various options for sedation regimens considered (Table 13.3) [2].

A final component of the presedation assessment is the establishment of when the child last had any oral intake (nil per os or NPO status). Recently, the need to adhere to strict NPO guidelines for procedural sedation has been challenged, particularly by those working in acute-care environments such as emergency rooms where procedures may need to be performed more urgently [3–6]. In specific cases in the Pediatric ICU patient, such as patients who have recently eaten, those with comorbid conditions which affect gastric emptying, those with altered mental status or impaired airway protective reflexes, and those with preexisting problems with respiratory or cardiovascular function, the safest way to proceed may include a rapid sequence induction and endotracheal intubation to provide airway protection during the procedure.

Given that any of the agents used for procedural sedation and analgesia can have deleterious effects on physiologic functions, patients should be monitored in accordance with guidelines set forth by the American Academy of Pediatrics (AAP) and/or the ASA during and following the use of these agents [3, 7, 8]. Although the PICU provides the optimal environment for the monitoring of a patient's physiologic functions, this monitoring should be continued when patients are transported out of the PICU [3, 7].

Table 13.3 Suggested guidelines for dosing of sedative and analgesic agents[a]

Agent	Dose	Comments
Fentanyl	2–3 μg/kg/h	Modulates the postsurgical and sympathetic stress response thereby blunting increases in pulmonary vascular resistance (PVR). May have utility in neonates and infants at risk for pulmonary hypertension following surgery for congenital heart disease. Has limited effects on cardiac output and mean arterial pressure. May result in mild to moderate negative chronotropic effects
Morphine	10–30 μg/kg/h	Cost-effective agent for sedation. Hemodynamic effects are generally related to vasodilation of capacitance vessels and a decrease in preload. These effects are exaggerated in the setting of hypovolemia. Delayed development of tolerance and less withdrawal issues when compared to fentanyl
Remifentanil	0.1–0.3 μg/kg/min	Short (4–8 min) and consistent half-life across all age groups including neonates and infants due to esterase metabolism. Use for prolonged (more than 24 h) sedation limited by the rapid development of tolerance and cost
Midazolam	0.05–0.15 μg/kg/h	Abundant clinical experience as an agent for PICU sedation. Metabolism by the P_{450} may result in prolonged half-life in patients with hepatic dysfunction. Presence of an active metabolite may result in prolonged sedation with long-term administration. Generic form limits cost when compared with other agents
Lorazepam	0.025–0.05 μg/kg/h	Limited clinical experience as an agent for sedation in the PICU population. Generic preparations limit cost. A major consideration is the accumulation of its diluent, propylene glycol. Metabolism by glucuronyl transferase limits changes in pharmacokinetics even with hepatic dysfunction
Ketamine	1–2 μg/kg/h	Endogenous catecholamine release results in bronchodilation and cardiovascular stability. However, may cause cardiovascular collapse in patients whose endogenous catecholamines are depleted as its primary direct effects are a decrease in myocardial function. Controversial effects on intracranial pressure (IP) and PVR although the recent literature demonstrates no deleterious effects
Pentobarbital	1–2 μg/kg/h	Second line agent after benzodiazepines and opioids. Alkaline pH leads to compatibility issues with other medications and may result in tissue irritation or sloughing of skin with extravasation. Hypotension may occur from vasodilatation and negative inotropic effects
Propofol	1–3 μg/kg/h	Rapid awakening upon discontinuation of the infusion. Solution has a high lipid content. Prolonged use (≥12 h) for sedation contraindicated in the PICU population due to risk of propofol infusion syndrome. Increasing data suggests that this may also occur in the adult population. May still be used in rare circumstances as a therapeutic agent for the treatment of increased ICP or status epilepticus; however, intermittent monitoring of acid–base status is suggested to monitor for toxicity
Haloperidol	0.06–0.45 μg/kg/day	Limited clinical experience in the pediatric population. Anecdotal data in the adult population suggest benefits of a decreased incidence of withdrawal and delirium with its use. May have a role for the treatment of agitation and delirium in the PICU population. Hypotension may result from α-adrenergic blockade. Additional adverse effects include lowering of the seizure threshold and the potential for cardiac arrhythmias due to prolongation of the QT interval
Dexmedetomidine	0.25–1 μg/kg/h	FDA approved for short-term (24 h) sedation in adults. Increasing experience in the pediatric population. Mechanism of action may limit delirium in the adult ICU setting. Adverse effects on hemodynamic function include bradycardia and hypotension

[a]The listed infusion rates are suggestions for starting doses. The actual infusion rate should be titrated up or down based on the patient's actual requirements and the response to the agent

Assessing the Depth of Sedation

During the use of sedative and analgesic agents, the repeated evaluation of the depth of sedation should be incorporated into the PICU routine with an increase or decrease in the doses used based on the patient's response. Clinical practice has included the move from the use of subjective measures and assessments made by healthcare providers to the use of formal pain and sedation scoring systems, which are monitored at regular intervals with the recording of physiologic vital signs.

These scoring systems include both those used during prolonged sedation during mechanical ventilation as well as those used for brief periods of time during procedural sedation.

The currently used PICU sedation scores evaluate either physiologic variables, an objective assessment of the patient's depth of sedation, or a combination of the two. One commonly used scale, the COMFORT score, combines the scoring of a patient's response or movement in addition to various physiologic parameters [11]. It relies on the measurement of alertness, respiration, blood pressure, muscle tone, agitation, movement, heart rate, and facial tension. This scoring system has been validated in the pediatric-aged patient and may have utility in the assessment of sedation during mechanical ventilation [11, 12]. However, scales that use physiologic parameters can be misleading in an ICU setting where alterations in vital signs can occur unrelated to the level of sedation. Furthermore, patients with cardiovascular dysfunction requiring vasoactive medications may not manifest increases in heart rate and blood pressure even in the presence of severe agitation or pain.

Ista et al. have recently proposed a modification of the original COMFORT score known as the COMFORT-B score which eliminates the use of physiologic variables and provides new cutoff points for the diagnosis of oversedation or undersedation [13]. Other scoring systems such as the Sedation-Agitation Scale (SAS) also eliminate the use of physiologic parameters. The SAS visually assesses the level of the patient's comfort and grades it from 1 (unarousable) to 7 (dangerous agitation such as pulling at the ETT) [14]. The Ramsay Scale, a sedation scale used commonly in the adult ICU population, also assigns a value based on the observation of the patient, but also uses a tactile stimulus (a glabellar tap) to distinguish between the deeper levels of sedation [15]. Scoring for the Ramsay Scale varies from 1 (awake, anxious, and agitated) to 6 (no response to a glabellar tap). The Hartwig score similarly uses a visual assessment of the patient, but as with the Ramsay Scale includes a response to a noxious stimulus, in this case, tracheal suctioning thereby eliminating its use in nonintubated patients [16]. Scales such as the Ramsay and the Hartwig that assess the response to a tactile stimulus require disturbing the patient to differentiate between the deeper levels of sedation. Additionally, scales that evaluate a patient's response to a stimulus or observe their behavior are not valid during the administration of neuromuscular blocking agents which prevent movement.

Various other scales have also been developed for assessing the patient during procedural sedation. The Observers Assessment of Alertness/Sedation (OAAS) scale has been validated in children, but has been shown to have a limited ability to differentiate between the deeper levels of sedation [17]. The Vancouver Sedative Recovery Scale appears to be better able to differentiate deeper levels of sedation, although it is likely too cumbersome to be easily utilized during short procedures [18]. More recently, Malviya et al. developed and validated the University of Michigan Sedation Scale (UMSS) [19]. This scale was developed to be a simple and efficient tool to assess depth of sedation over the entire sedation continuum and one that could easily be applied by various healthcare providers. It utilizes a simple scale ranging from 0 (awake and alert) to 4 (unresponsive).

However, none of these sedation scales meet all of the needs of the PICU provider. As such, there remains an interest in the use of monitoring technology to assess the depth of sedation through the analysis of the electroencephalogram (EEG). The bispectral index (BIS monitor) (Aspect Medical, Newton, MA) uses a programmed algorithm to evaluate the processed EEG pattern and provide a numeric value ranging from 0 (isoelectric) to 100 (awake with eyes open). Its predominant clinical use has been to monitor the effects of general anesthesia.

Although still somewhat controversial, it has been suggested that maintenance of a BIS value less than 60–70 correlates with a low probability of intraoperative awareness [20, 21]. The BIS monitor has been used in settings outside of the operating room for assessment during procedural sedation or mechanical ventilation [22–30]. Gill et al. compared BIS values with Ramsay sedation

scores in 37 adults who received procedural sedation in the emergency room setting [22]. There was a wide variability in BIS values at similar sedation scores. The BIS was most effective at differentiating moderate-to-deep sedation from general anesthesia.

Brown McDermott et al. compared BIS values with UMSS scores during procedural sedation administration in 86 children less than 12 years of age [23]. Although there was a good correlation between the BIS value and the sedation score, a wide variability in the range of BIS values for each level of sedation was again noted. The BIS monitor was ineffective at determining the depth of sedation with ketamine or a combination of oral chloral hydrate, hydroxyzine and meperidine.

Despite these shortcomings, the BIS monitor may be able to effectively identify patients who are becoming too deeply sedated and may therefore be at risk for adverse respiratory events. Motas et al. demonstrated that the depth of sedation as judged by the BIS monitor was predictive of adverse airway events during the administration of procedural sedation (either propofol, midazolam or pentobarbital) by nonanesthesiologists [24].

BIS monitoring has also been evaluated as a means of evaluating the depth of sedation during prolonged mechanical ventilation. Although the results have been somewhat mixed, the majority of reports have demonstrated a clinically acceptable correlation between the BIS monitor and commonly used ICU sedation scores including the Ramsay or the COMFORT score [25–31].

The more recent versions of the BIS probe incorporate a sensor to reduce electromyographic (EMG) interference. The BIS algorithm was developed for use with propofol or the potent inhalational anesthetic agents which work through the γ-amino butyric acid (GABA) system. Therefore, the BIS monitor is not accurate with the administration of etomidate or agents which act through the *N*-methyl-d-aspartate (NMDA) system including xenon or nitrous oxide [32–34]

Despite these issues, our clinical experience suggests that some form of depth of sedation monitoring may be particularly efficacious in situations that preclude the use of conventional ICU scoring systems (patients receiving neuromuscular blocking agents and/or medications that may alter heart rate and blood pressure responses) [35–38]. The BIS monitor provides a continuous numeric readout using a simple 0–100 scale that is immediately available at the bedside as opposed to sedation scoring systems that provide only an intermittent assessment and require time to assess and tabulate the various parameters

Basic Principles

Several variables should be considered when providing therapeutic sedation and analgesia for the PICU patient. Unfortunately, there is limited evidence-based medicine from which to develop guidelines for the use of sedative and analgesic agents in the PICU setting (Table 13.3). There are still limited studies which evaluate the pharmacokinetics and pharmacodynamic properties of analgesic and sedative drugs in critically ill infants and children [39–41]. Pharmacokinetic studies are generally performed in healthy adult volunteers with the extrapolation of these results to infants and children. The comorbidities present in the PICU may affect several variables including volume of distribution and elimination half-life thereby further altering the pharmacokinetics or these agents. Additional variabilities in the PICU setting are likely to result from drug–drug interactions, end-organ (hepatic, renal) failure or dysfunction, malnutrition, low plasma proteins with altered drug binding, alterations in uptake of the medication if nonintravenous routes are used, and alterations in drug distribution. Pharmacogenetic factors may also affect responses to medications as we are beginning to learn that there are genetic differences that affect the way we respond to acute illness and the way we metabolize various medications [42, 43].

An example of such variability in the PICU population is demonstrated by an evaluation of fentanyl infusion requirements during mechanical ventilation in neonates and infants [44]. The fentanyl infusion requirements varied from 0.47 up to 10.3 μg/kg/h to achieve a similar effect. Therefore, it is not feasible to approach the provision of sedation and analgesia in the PICU patient using a "cookbook." The dosing recommendations provided in this chapter for the specific medications discussed are meant only as guidelines for starting doses which may be titrated to effect [45].

Despite the potential difficulties and risks of sedation and analgesia in the PICU patient, there may be significant benefits. Aside from humanitarian concerns, clinical trials have reported decreases in morbidity and mortality based on the analgesic regimen following cardiovascular surgery for congenital heart disease in neonates and infants [46, 47]. These effects are postulated to be the result of blunting of the endogenous physiologic stress response thereby decreasing release of endogenous catecholamines and adrenal cortical hormones. This physiologic stress response, when excessive, may have deleterious end-organ effects. Analgesia and sedation may facilitate cardiac and respiratory support such as permissive hypercapnia, reverse I:E ratio ventilation, high-frequency ventilation, and extracorporeal support. It may also provide therapeutic benefits in the treatment of intracranial hypertension or to modulate pulmonary vascular resistance (PVR) in patients at risk for pulmonary hypertension and limit the need for neuromuscular blocking agents and their associated adverse effects [48].

Choice of Agent and Route of Delivery

The three primary decision points for sedation and analgesia in the PICU include the agent, its route of administration, and its mode of administration. As no agent will be effective in every patient or scenario, basic knowledge regarding the various agents allows the healthcare provider to switch from one agent to another when the first line drug is either ineffective or associated with adverse effects. In the remainder of this chapter, a brief discussion of each agent is provided and its use in the PICU setting discussed.

Although the intravenous route is chosen in most clinical scenarios, alternative routes may be required in specific clinical scenarios or patient populations. Furthermore, there is expanding knowledge and interest regarding the use of alternative routes especially inhalational anesthesia or subcutaneous administration in the PICU setting. This chapter will review the clinical experience and the pertinent literature associated with the common sedatives and analgesics in the PICU.

Inhalational anesthetic agents

The potent inhalational anesthetic agents are used on a daily basis during the perioperative period to provide amnesia and analgesia during major surgical procedures. Based on their chemical structure, these agents can be divided into alkanes such as halothane or substituted ethers. The substituted ethers include either methyl, ethyl ethers such as isoflurane, desflurane, and enflurane or methyl, isopropyl ethers such as sevoflurane. The characteristics of these agents which may make them useful agents for ICU sedation include a rapid onset, rapid awakening upon discontinuation, and the ability to rapidly control the depth of sedation. The potent inhalational anesthetic agents also provide specific therapeutic end-organ effects including bronchodilatation, myocardial preconditioning, and cerebral protection. Although experience with use of the potent inhalational anesthetic agents for ICU sedation in the United States is limited, certain centers in Europe and the United Kingdom have reported favorable experiences with these agents in adult ICU patients [49–52]. Despite the fact that these agents are all considered in the category of the potent inhalational anesthetic agents, their physiologic effects are distinctly different.

Various adverse physiologic effects have been reported with halothane including a negative inotropic and chronotropic effect on myocardial function, the potential for a proarrhythmogenic effect especially in the setting of increased catecholamines or when used in conjunction with

other medications (e.g., aminophylline), and the potential for the development of hepatitis related to an immunologic reaction directed against the oxidative metabolite, trifluoroacetic acid [53, 54]. Although hepatitis may occur with the other inhalational anesthetic agents including isoflurane, its incidence is less with isoflurane due to its limited metabolism of 0.2% compared with that of halothane (15–20%).

Given the potential for adverse effects on myocardial function and its association with perioperative cardiac arrests in infants and children, halothane is no longer in use in the United States. Likewise, given its adverse effect profile and the introduction of newer agents, enflurane is disappearing from anesthetic practice throughout the world. Adverse effects with the prolonged administration of enflurane include negative inotropism and the release of fluoride during metabolism. Plasma fluoride concentrations in excess of 50 μmol/L can have deleterious effects on renal function with a decreased glomerular filtration rate and renal tubular resistance to vasopressin with nephrogenic diabetes insipidus. Three to five percent of sevoflurane also undergoes metabolism and like enflurane, sevoflurane is highly substituted with fluoride. Therefore, its prolonged administration can also result in elevated serum fluoride concentrations.

Desflurane is the newest of the inhalational anesthetic agents. Its beneficial properties include low blood:gas and blood:fat solubility coefficients thereby resulting in a rapid onset and rapid awakening upon its discontinuation. When compared with propofol for postoperative sedation of adults requiring mechanical ventilation, there was a shorter and more predictable emergence time and a faster return of mental recovery with desflurane compared to propofol with no difference in the incidence of adverse effects [51]. Drug costs were lower with desflurane than with propofol (95€ for desflurane vs. 171€ for propofol per 24 h) with additional costs of soda lime (5€) being comparable to the costs of infusion tubing for propofol (2.5€). Adverse effects with desflurane include hypotension primarily from peripheral vasodilatation, rebound tachycardia from stimulation of the sympathetic nervous system which occurs primarily with rapid increases in the inhaled concentration or the use of inspired concentrations in excess of 6% (a concentration not likely to be required in the ICU setting), direct irritant effects on the airway thereby making it less than optimal in patients with airway hyperreactivity, and rare reports of carbon monoxide formation due to desflurane's interaction with dessicated soda lime.

Additional concerns with all of the inhalational anesthetic agents include their potential as a trigger agent for malignant hyperthermia, cost issues, effects on intracranial pressure (ICP), and alterations of the metabolism of other medications. As nonspecific vasodilators, all of the inhalational anesthetic agents cause cerebral vasodilatation resulting in an increase in ICP in patients with compromised intracranial compliance. Cerebral vasodilatation can be partially blunted by hyperventilation to a $PaCO_2$ of 25–30 mmHg [55, 56]. The inhalational anesthetic agents alter the metabolism of several mediations which may be used in the PICU setting including lidocaine and other local anesthetic agents, β-adrenergic antagonists, and benzodiazepines [57].

To date, there is a limited experience with the use of the potent inhalational anesthetic agents for sedation in the PICU setting. Arnold et al. reported their experience with isoflurane for sedation in ten pediatric patients (3 weeks to 19 years), who required endotracheal intubation and mechanical ventilation [58]. The duration of isoflurane administration ranged from 29 to 769 h (245 ± 225 h). Sedation was initiated with isoflurane at an inspired concentration of 0.5% and adjusted in 0.2% increments as needed. There was adequate sedation 75% of the time, excessive sedation 4% of the time, and inadequate sedation 21% of the time. In the five patients who received isoflurane for at least 96 MAC (minimum alveolar concentration)-hours, there were no differences in blood urea nitrogen, serum creatinine, osmolality, bilirubin, and alanine aminotransferase between time 0 and 96 h. The duration of isoflurane administration correlated directly with the plasma fluoride concentration. Five of the patients, who had received greater than 70 MAC-hours, manifested

signs and symptoms suggestive of withdrawal including agitation and nonpurposeful movements when the isoflurane was discontinued.

Despite the potential advantages of using the potent inhalational anesthetic agents for sedation in the ICU setting, logistic problems regarding delivery of these agents may limit applicability in the ICU setting [50].

Given the problems with the devices and techniques currently available for the delivery of the potent inhalational anesthetic agents in the ICU setting, novel means of delivering these agents are needed. The Anesthetic Conserving Device or "AnaConDa®" (ACD, Hudson RCI, Upllands Väsby, Sweden) is a modified heat-moisture exchanger which may allow a simplified means of administering the inhalational anesthetic agents in the ICU setting. The device is placed between the Y-piece of the ventilator circuit and the ETT. There is also a port at the end of the device just proximal to its attachment to the ETT which allows gas sampling and monitoring of the agent concentration. The desired inspired concentration is titrated by adjusting the infusion rate on the syringe pump based on the manufacturer's recommendations. Exhaled isoflurane is adsorbed to the lipophilic carbon particle filter in the device and redelivered to the patient thereby limiting environmental pollution.

Sackey et al. evaluated the ACD in the ICU setting in 40 adult patients requiring sedation for more than 12 h [59]. The patients were randomized to sedation with isoflurane administered with the ACD or a continuous infusion of midazolam. The inspired isoflurane concentration was started at 0.5% (infusion rate on the syringe pump of 1–3.5 mL/h according to the manufacturer's recommendations) while midazolam was infused at 0.02–0.05 mg/kg/h. The infusion rates were adjusted as needed and opioids administered for analgesia. The percentage of time within the desired level of sedation was similar between the two groups (54% with isoflurane and 59% with midazolam) with no difference in opioid requirements or the need for bolus doses of sedative agents. The time to extubation (10 ± 5 vs. 252 ± 271 min) and the time to follow verbal commands (10 ± 8 vs. 110 ± 132 min) were shorter with isoflurane than with midazolam. Anecdotal experience with the device has also been reported in three pediatric patients who required sedation during mechanical ventilation or in the treatment of status epilepticus [60].

Benzodiazepines

The benzodiazepines remain the most commonly used agent for sedation during mechanical ventilation in the PICU patient. These agents produce amnesia, anxiolysis, and sedation through their effects on the inhibitory neurotransmitter, GABA. Benzodiazepines bind to the α-subunit of the GABA receptor thereby facilitating binding of the GABA molecule to the β-subunit. This interaction increases chloride conduction across the neuronal membrane resulting in hyperpolarization. Benzodiazepines in common clinical use in the United States for sedation in the PICU include midazolam and lorazepam. Diazepam was formerly a commonly used agent for sedation in both pediatric and adult ICUs. Its high lipid solubility results in a rapid onset of action; however, its low water solubility requires administration in a solution of propylene glycol which can cause pain and thrombophlebitis when administered through a peripheral vein. Diazepam is also available in a lipid formulation which has been shown to alleviate the discomfort associated with the intravenous administration of the propylene glycol preparation [61, 62]. Diazepam has fallen out of favor as an agent for sedation in the PICU setting because of its prolonged duration of action as well as its metabolism to active compounds with elimination half-lives that far exceed the parent compound. With repeated administration, the metabolites can accumulate and result in prolonged sedation and delayed awakening once the drug is discontinued.

Midazolam is an imidazobenzodiazepine with a rapid onset of action and a short elimination half-life [63]. Clinical experience and years of its use have demonstrated the efficacy of continuous midazolam infusions for sedation in the PICU patient in doses ranging from 0.05 to 0.2 mg/kg/h [64–66]. Its availability in generic form makes it a cost-effective form of sedation.

Rosen and Rosen retrospectively reviewed their experience with midazolam infusions for

sedation during mechanical ventilation in 55 pediatric patients [66]. Midazolam dosing was initiated with a bolus dose of 0.25 mg/kg followed by a continuous infusion of 0.4–4 μg/kg/min (0.02–0.2 mg/kg/h). Midazolam was effective in all patients without significant hemodynamic effects. The authors noted that midazolam became ineffective in one patient following the institution of ECMO and related this to midazolam binding to the surface of the membrane oxygenator. Similar efficacy has been reported by other investigators [67].

Although intravenous administration is generally the route chosen in the PICU patient, midazolam remains unique among many of the other agents used for sedation in the ICU setting in that alternative, nonintravenous routes of delivery have been used clinically including oral, rectal, transmucosal (nasal, rectal, sublingual), and subcutaneous administration [68–72]. With all of these nonintravenous routes except for subcutaneous administration, increased doses are required due to decreased bioavailability.

In many centers in the United States, oral midazolam is currently the preferred agent for premedication in the operating room. Doses for oral administration have ranged from 0.25 up to 0.7 mg/kg. The primary disadvantage of oral administration is that the IV preparation (5 mg/mL) is generally used which contains the preservative, benzyl alcohol, thereby giving the drug a very bitter taste.

A commercially available preparation of midazolam in a cherry-flavored solution for oral administration is available (Versed syrup, Roche Laboratories Inc, Nutley, NJ). Because of the control of pH during the manufacturing process, clinical data suggest that effective sedation can be achieved with doses as low as 0.25 mg/kg compared to the 0.5–1.0 mg/kg doses reported when using the IV preparation diluted in other solutions for oral administration [73]. Additional nonparenteral administration routes include intranasal and sublingual administration. The dose (0.2–0.4 mg/kg) is lower and the onset more rapid when compared to the oral route as midazolam is rapidly absorbed across both mucosal surfaces with sedation occurring in as little as 5–10 min. With intranasal administration, the preservative, benzyl alcohol, may burn the nasal mucosa. This is avoided with sublingual administration, but issues of taste and patient cooperation may limit the usefulness of this route.

Midazolam is metabolized by isoforms of the hepatic P_{450}3A enzyme system to the major hydroxylated metabolite, 1-OH midazolam. 1-OH midazolam is approximately equipotent with the parent compound. It undergoes further hepatic metabolism via the glucuronyl transferase system to 1-OH midazolam-glucuronide, a water soluble metabolite, which is renally excreted. In the presence of renal insufficiency, 1-OH midazolam-glucuronide accumulates thereby potentiating the effects of midazolam [74]. Several factors including age and underlying illness may also alter midazolam pharmacokinetics. With metabolism dependent on the hepatic P_{450} system, clearance changes from infancy to adult age and with alterations in hepatic function [75, 76]. Additional changes may occur related to critical illness. In a cohort of 21 PICU patients, midazolam clearance was significantly longer (5.5 ± 3.5 h) than that reported in healthy age-matched children (1.2 ± 0.3 h) [77, 78].

Lorazepam is a water soluble benzodiazepine that is metabolized by glucuronyl transferase. Its metabolites are pharmacologically inactive. Medications known to alter the P_{450} system (anticonvulsants, rifampin, cimetidine) do not alter lorazepam's pharmacokinetics. In advanced liver disease, phase II reactions (glucuronyl transferase) are better preserved than phase I reactions (P_{450} system) so that the pharmacokinetics of lorazepam remains unchanged. The Society of Critical Care Medicine guidelines for sedation of adult patients in the ICU setting has recommended lorazepam as the preferred sedative [79].

In comparison to midazolam, there are fewer reports regarding the use of lorazepam for sedation in both the pediatric and the adult ICU population [80, 81]. When comparing lorazepam with midazolam in adult ICU patients, the mean infusion rates to achieve adequate sedation were 0.06 mg/kg/h for lorazepam and 0.15 mg/kg/h for midazolam [80]. There were fewer infusion

rate adjustments per day with lorazepam than with midazolam (1.9 for lorazepam vs. 3.6 for midazolam). The mean time to return to baseline mental status was shorter with lorazepam (261 min with lorazepam vs. 1,815 min with midazolam).

Lugo et al. suggested the use of enteral lorazepam to decrease intravenous midazolam dosing requirements and drug costs during mechanical ventilation in a cohort of 30 infants and children [82]. Midazolam was used for sedation until the requirements were stable for 24 h. Enteral lorazepam was dosed at 1/6th of the total daily intravenous midazolam dose. There was a significant reduction in midazolam requirements on day 1 and by day 3, the midazolam infusion was discontinued in 24 of 30 patients. Enteral lorazepam has also been successfully used for the treatment or prevention of withdrawal following the prolonged administration of intravenous benzodiazepines for sedation during mechanical ventilation in the PICU population [83].

Each milliliter of the intravenous lorazepam solution (2 mg lorazepam per mL of solution) contains 0.8 mL or 800 mg of propylene glycol. With prolonged or high-dose intravenous administration, issues may arise related to the diluent used in the intravenous formulations, propylene glycol [84–86]. Signs and symptoms of propylene glycol toxicity include metabolic acidosis, renal failure/insufficiency, mental status changes, hemolysis, and an elevated osmolar gap. Propylene glycol is metabolized in the liver to lactic acid and pyruvic acid, which, in part, accounts for the lactic acidosis. Propylene glycol is also excreted unchanged in the urine making toxicity more likely in patients with renal insufficiency. Attention to the propylene glycol infusion rate and periodic calculation of the osmolar gap (measured minus calculated serum osmolarity) may be indicated during high dose or prolonged lorazepam infusions. An increasing osmolar gap has been shown to be predictive of increasing serum propylene glycol levels [86]. As neonates and preterm infants are unable to handle propylene glycol related to hepatic and renal immaturity, continuous infusions of lorazepam are not recommended in this population.

In a cohort of 11 PICU patients, who received lorazepam infusions ranging from 0.1 to 0.33 mg/kg/h for 3–14 days, the propylene glycol concentration increased from 86 ± 93 μg/mL at baseline to 763 ± 660 μg/mL at the completion of the infusion [87]. The plasma propylene glycol concentration correlated with the cumulative dose of lorazepam. No end-organ effects, related to the increased propylene glycol concentrations such as acidosis or hyperosmolarity, were noted in these patients. The authors recommended periodic monitoring for lactic acidosis and hyperosmolarity during prolonged lorazepam infusions

Etomidate

Etomidate (Amidate, Abbott Pharmaceuticals) is an intravenous anesthetic agent, introduced into clinical practice in 1972. Its primary effects of sedation and amnesia are mediated through the GABA inhibitory neurotransmitter system. Unlike other sedative and hypnotic agents, only the R(+) enantiomer has clinical effects. Following intravenous administration, loss of consciousness is rapid (15–20 s) and as with propofol and the barbiturates, its duration of action following a single bolus dose is related to redistribution rather than metabolism and clearance. Etomidate undergoes hepatic metabolism with an elimination half-life that varies from 2.9 to 5.3 h [88]. Beneficial CNS effects include a decrease of the cerebral metabolic rate for oxygen ($CMRO_2$), cerebral blood flow (CBF), and ICP. Cerebral perfusion pressure (CPP) is maintained because of minimal effects on myocardial function. In an animal model comparing the hemodynamic effects of an induction dose of etomidate (0.3 mg/kg) with propofol (2.5 mg/kg), no hemodynamic changes were noted with etomidate while propofol decreased systolic blood pressure by 19.9%, diastolic blood pressure by 25.3%, cardiac output by 17.3%, and systemic vascular resistance by 11.6% [89].

Contrary to a relatively large clinical experience in the adult population, there are limited data regarding the use of etomidate in pediatric-aged patients [90–93]. Despite the relatively limited clinical data regarding this agent, recent reviews continue to suggest its use as a single

bolus dose for critically ill pediatric patients requiring endotracheal intubation [94].

Like the barbiturates and propofol, etomidate results in a dose-dependent depressant effect on respiratory function and can result in apnea depending on the dose used, concomitant use of other medications, and the patient's underlying status. Lehman and Mainka evaluated the effects on CO_2 responsiveness of alfentanil (15 μg/kg) after premedication with etomidate (10 mg), diazepam (5 mg), or droperidol (5 mg) in adult volunteers [95]. All patients demonstrated a shift of the CO_2 response curve to the right without a change in the slope. These effects dissipated in 60 min. No difference was noted between etomidate and the other two premedications. Although both methohexital (1.5 mg/kg) and etomidate (0.3 mg/kg) decrease the slope of the CO_2 response curve, the effect has been shown to be more pronounced with methohexital [96]. Despite this relative sparing of respiratory function, an increased incidence of apnea has been reported following etomidate in patients pretreated with either opioids of benzodiazepines [97, 98].

Etomidate's place as an agent for procedural sedation results from its negligible effects on myocardial function, even in patients with significant alterations in myocardial function. It has beneficial effects on the CNS which include a reduction of the $CMRO_2$ leading to cerebral vasoconstriction, decreased CBF, and decreased ICP. Renou et al. noted a 34% decrease in CBF following the administration of etomidate in healthy adults [99]. As a result of the decreased $CMRO_2$ and CBF, etomidate decreases ICP while maintaining mean arterial pressure thereby increasing cerebral perfusion pressure [100]. Despite its ability to lower CBF and ICP, induction or sedative doses of etomidate can produce increased EEG activity and epileptic-like EEG potentials in patients with underlying seizure disorders [100–103].

Myoclonic movements are a frequently observed effect following the rapid intravenous administration of etomidate [104]. Although these movements may simulate tonic-clonic seizure activity, no epileptiform discharges are noted. It has been suggested that the myoclonic movements are of spinal origin resulting from disinhibition of inhibitory neuronal pathways. Pretreatment with fentanyl, benzodiazepines, or a small dose of etomidate has been shown to be effective in decreasing the incidence of myoclonus. A trial of etomidate for sedation during computerized tomography was discontinued due to an unacceptably high incidence of involuntary motor movements preventing completion of the scan [105]

The most significant concern with etomidate and the factor that limits its long-term administration in the ICU setting is its effects on the endogenous production of corticosteroids. This effect was identified when an increased risk of mortality was noted in adult ICU patients who were sedated with a continuous infusion of etomidate [106]. Etomidate inhibits the enzyme, 11-β hydroxylase, which is necessary for the production of cortisol, aldosterone, and corticosterone. To date, significant controversy surrounds the clinical significance of the adrenal suppression following a single induction dose of etomidate, with some authors calling for the abandonment or at least a reevaluation of the use of etomidate [107–109]. The duration of the adrenal suppression produced by a single induction dose of etomidate has varied from study to study.

Duthie et al. demonstrated a decrease in plasma cortisol levels 1 h following an induction dose of etomidate; however, at 24 h no difference was noted between those patients receiving etomidate and those receiving other induction agents [110]. Other authors have suggested a more prolonged suppression of adrenocortical function. Donmez et al. evaluated the effects of etomidate on plasma cortisol levels in children following cardiothoracic surgery [111]. The patients were randomized to anesthetic induction with either ketamine (1 mg/kg) or etomidate (0.3 mg/kg). Plasma cortisol levels were significantly lower during cardiopulmonary bypass, at the end of the operation, and at 24 h in the group that received etomidate vs. ketamine. Absalom et al. reported a similar effect with ongoing suppression of adrenal function at 24 h in a cohort of critically ill adult patients [112]. In a cohort of 40 critically ill adult patients, the incidence of adrenal insufficiency following a

single dose of etomidate was 80% at 12 h, 9% at 48 h, and 7% at 72 h [113]. Despite these findings, no difference in outcome was reported following etomidate administration in a cohort of 159 adult patients with septic shock [114].

Perhaps the most compelling data against the use of etomidate, at least in patients with possible sepsis, comes from the CORTICUS trial [115]. Post hoc analysis revealed that patients who had received etomidate had a significantly higher mortality rate. Additionally, this increased risk of mortality was not prevented by the administration of corticosteroids. These data suggest that etomidate should be avoided in patients with sepsis or septic shock.

In addition to its effects on adrenal function, reports regarding continuous etomidate infusions with increased mortality suggested an association with infectious complications. Neutrophils incubated in vitro with etomidate demonstrate depressed chemiluminescence, an index of oxygen-free radical generation, suggesting that etomidate may interfere with white blood cell bactericidal activity [116].

Additional reported adverse effects with etomidate, related to the drug itself or the diluent, include anaphylactoid reactions, pain on injection, and an increased incidence of nausea and vomiting [117]. Issues related to the carrier vehicle (propylene glycol) include pain on injection, thrombophlebitis, and propylene glycol toxicity [118]. The incidence of pain on injection has been reported to be as high as 50%.

A newer formulation, which contains etomidate dissolved in a fat emulsion of medium and long-chair triglycerides, may limit the occurrence of injection pain and thrombophlebitis [119]. As with lorazepam, issues may arise with repeated dosing or continuous infusions of etomidate because of the diluent, propylene glycol (please note that given concerns regarding adrenal suppression, long-term etomidate infusions are no longer used in the ICU setting) [120–122].

Despite these issues, given its beneficial effects on CNS dynamics and myocardial function, etomidate has yet to be abandoned in critically ill patients and may still play a role as an effective agent to provide sedation and amnesia during endotracheal intubation [123]. Its lack of cardiovascular effects makes it particularly valuable in patients who may not tolerate a decrease in systemic vascular resistance or myocardial contractility. Given its effects on cerebral dynamics, it also should be considered for patients with increased ICP with or without associated myocardial dysfunction. Although of limited utility for the provision of procedural-sedation outside of endotracheal intubation, as with several other sedative/analgesic agents, nonintravenous routes of delivery including oral, buccal and rectal administration have been investigated [124–126].

Ketamine

Ketamine was introduced into clinical practice during the 1960s [127]. Ketamine's sedative, analgesic, and amnestic properties are mediated through agonism of opioid receptors and antagonism of NMDA receptors. A unique attribute of ketamine, which separates it from the majority of other agents discussed in this chapter, is the provision of both amnesia and analgesia. Ketamine contains a chiral carbon in its structure and the preparation currently used most commonly in clinical practice is a racemic mixture of the two optical isomers [S(+) and R(−)].

In the United Kingdom and Europe, the enantiomer, S(+) ketamine, is available with the suggestion from preliminary clinic trails that it may provide effective analgesia and sedation while limiting adverse effects including emergence phenomena (see below). Metabolism of ketamine occurs primarily by hepatic *N*-methylation to norketamine, which retains approximately one third of the analgesic and sedative properties of the parent compound. Given its dependence on hepatic metabolism, doses should be adjusted in patients with hepatic dysfunction. Dose adjustments may also be required in patients with renal dysfunction since norketamine is dependent on renal elimination.

Beneficial properties of ketamine include preservation of cardiovascular function, limited effects on respiratory mechanics, and maintenance of central control of respiration. These properties make it an effective and popular agent in the arena of procedural sedation during painful, invasive procedures in the spontaneously

breathing patient [10]. Incremental doses (0.5–1 mg/kg) can be administered every 1–2 min and titrated to achieve the desired level of sedation and analgesia while generally maintaining spontaneous ventilation.

Given its effects at the opioid and NMDA receptors, there is growing interest in the use of ketamine for the management of acute pain. When coadministered in low doses during morphine analgesia, ketamine has been shown to reduce postoperative opioid consumption and lower opioid-related adverse effects following major surgical procedures in the adult population [128–131]. As NMDA receptor stimulation may be one factor resulting in the development of tolerance to opioid-induced sedation and analgesia, there is interest in the potential benefits of using a low-dose ketamine infusion to delay tolerance during prolonged ICU infusions of morphine and other opioids.

Ketamine's popularity in the arena of procedural-sedation, especially painful invasive procedures, relates to its beneficial effects on cardiac and respiratory function. Ketamine generally increases heart rate and blood pressure as well as provides bronchodilatation due to the release of endogenous catecholamines [132]. Although the indirect sympathomimetic effects from endogenous catecholamine release generally overshadow ketamine's direct negative inotropic properties, cardiovascular collapse may occur in patients with diminished myocardial contractility [133, 134].

An issue of potential concern and ongoing controversy regarding ketamine is its effects on pulmonary vascular resistance (PVR) [135–138]. Williams et al. evaluated the effects of ketamine on PVR during sevoflurane anesthesia (0.5 MAC) and spontaneous ventilation in 15 infants and children with pulmonary hypertension (mean PA pressure ≥25 mmHg, baseline PVR index of 11.3 Woods units) [139]. There were no significant changes in mean systemic arterial pressure, systemic vascular resistance index, mean pulmonary artery pressure, PVR index, cardiac index, and $PaCO_2$. The safety of ketamine in patients with congenital heart disease is further evidenced by experience with its use during spontaneous ventilation for sedation during cardiac catheterization [140, 141].

Ketamine has also been shown to have limited effects on several respiratory parameters including functional residual capacity, minute ventilation, and tidal volume [142, 143]. The release of endogenous catecholamines generally results in improved pulmonary compliance, decreased resistance, and prevention of bronchospasm [144, 145]. Although generally effective in allowing maintenance of protective airway reflexes and spontaneous ventilation, like any sedative/analgesic/general anesthetic agent, ketamine can result in loss of protective airway reflexes, gastric aspiration, and apnea [146–148].

An additional area of controversy surrounding ketamine is its effect on ICP. These effects may be indirect, secondary to changes in $PaCO_2$, or the result of a direct effect on the cerebral vasculature [149–152]. More recent data from both animal and human studies have shown no change or even a decrease in ICP following ketamine [153, 154].

Ketamine in doses of 1.5, 3, or 5 mg/kg decreased ICP when administered to adult head trauma patients who were sedated with propofol and mechanically ventilated to maintain a $PaCO_2$ of 35–38 mmHg [155]. The ICP decreased by 2 ± 0.5, 4 ± 1, and 5 ± 2 mmHg with doses of 1.5, 3, and 5 mg/kg respectively. There was no change in CPP. Similar results were reported by others [156, 157].

An additional potentially beneficial effect of ketamine in patients with CNS trauma is an alteration of transmembrane calcium and magnesium currents through its effects on the NMDA receptor [158].

Another somewhat controversial issue related to the CNS effects of ketamine is its use in patients with an underlying seizure disorder. EEG recordings in children and laboratory animals during ketamine administration demonstrate increased frequency and amplitude with occasional paroxysmal seizure activity [159, 160]. However, no clinical evidence of seizure activity has been reported with ketamine administration. Studies in laboratory animals have demonstrated the anticonvulsant effects of ketamine and there is at least one clinical report as well as animal data describing its use for the treatment of refractory status epilepticus [161–163].

With everyday clinical use, the adverse effect of ketamine that tends to attract the most attention is its potential to cause emergence phenomena or hallucinations. The ketamine solution that is in common clinical use is a racemic mixture of the two optically active enantiomers. The single enantiomer form, S(+) ketamine, has been released outside of the United States for clinical use [164–167]. The initial clinical trials have demonstrated that S(+) ketamine is twice as potent as the racemic formulation and offers the clinical advantages of fewer psychomimetic effects, less salivation, and a shorter recovery time [167].

To date, there are only anecdotal reports involving small case series regarding the use of a ketamine infusion for sedation of the PICU patient during mechanical ventilation [168–170]. The largest series included ten patients, ranging in age from 1 week to 30 months. A ketamine infusion, 1 mg/kg/h in five patients and 2 mg/kg/h in the other five patients, was used to provide sedation and analgesia following cardiac surgery in ten pediatric patients [169]. Supplemental doses of midazolam were administered as needed. The two groups had similar and acceptable levels of sedation. No adverse effects were noted.

Although it may never become a first-line agent for sedation in the PICU patient during mechanical ventilation, ketamine may be useful in patients who develop adverse cardiovascular effects with opioids or benzodiazepines, for the provision of sedation with the preservation of spontaneous ventilation when using noninvasive ventilation techniques, in patients with status asthmaticus in whom the release of endogenous catecholamines following ketamine administration may provide some therapeutic impact, in low doses by continuous infusion to delay or prevent the development of tolerance to opioids related to its effects at the NMDA receptor, and during the performance of brief, painful invasive procedures in the spontaneously breathing patient [166, 171, 172].

Propofol

Propofol is an alkyl phenol compound (2,6-diisopropylphenol) with general anesthetic properties. Although its chemical structure is distinct from that of other intravenous anesthetic, its mechanism of action is similar as it acts through the GABA system [173]. Propofol facilitates the binding of GABA to membrane-bound receptors thereby increasing chloride conductance. Although propofol was initially introduced into anesthesia practice for the induction and maintenance of anesthesia, its rapid onset and recovery times led to its eventual use for sedation in the ICU setting [174, 175]. When compared with midazolam for sedation in adult patients, propofol has been shown to provide shorter recovery times, improved titration efficiency, reduced posthypnotic obtundation, and faster weaning from mechanical ventilation [176].

Like the barbiturates and etomidate, propofol decreases $CMRO_2$ leading to reflex cerebral vasoconstriction and lowering of ICP [177].

Several animal studies have confirmed the potential beneficial effects of propofol on cerebral dynamics. In an animal model of cytotoxic and vasogenic cerebral edema, propofol lowered ICP and maintained CPP in vasogenic cerebral edema, but had no effect in cytotoxic cerebral edema [178]. Watts et al. compared the effects of propofol and hyperventilation on ICP and somatosensory evoked potentials (SEPs) in an animal model of intracranial hypertension [179]. The ICP decrease and the SEP increase were greater with propofol than with hyperventilation.

Despite these animal data, there are conflicting results in regard to the effects of propofol on ICP from studies in humans. Although ICP is decreased in the majority of the studies, propofol's lowering of MAP may result in a decrease of the CPP [180]. Similar results have been reported in adults with traumatic brain injury or during cerebral aneurysm surgery [181–183].

If MAP is maintained at baseline with vasoactive agents, propofol may lower ICP and increase CPP. When propofol (2–4 mg/kg/h) was used for sedation during mechanical ventilation in ten adult patients with traumatic brain injury, ICP decreased by a mean of 2.1 mmHg at 2 h and the CPP increased by 9.8 mmHg at 24 h [184]. Additional beneficial effects of propofol in brain injury include animal data suggesting a protective effect of propofol in various types of

hypoxic-ischemic injury models as well as the preservation of the CBF reactivity to carbon dioxide [185–187].

When comparing the effects of propofol (2.5 mg/kg), etomidate (0.4 mg/kg), or thiopental (5 mg/kg) in 77 adults, respiratory resistance was lower after propofol [188]. Pizov et al. randomized a cohort of asthmatic and nonasthmatic patients to receive thiopental/thiamylal (5 mg/kg), methohexital (1.5 mg/kg), or propofol (2.5 mg) [189]. Following endotracheal intubation, auscultation was performed. In asthmatic patients, the incidence of wheezing was 45% with thiopental/thiamylal, 26% with methohexital, and 0% with propofol. In nonasthmatic patients, the incidence of wheezing was 16% with thiopental/thiamylal and 3% with propofol. Propofol's beneficial effects on airway reactivity are further supported by animal studies [190, 191]. In both an animal model and a human study, these beneficial effects were present only with the propofol solution that has ethylenediaminetetraacetic acid (EDTA) as the preservative and not the newer formulation containing sodium metabisulfite [192, 193].

Propofol's cardiovascular effects resemble those of the barbiturates with the potential for hypotension from peripheral vasodilation and negative inotropic properties. These effects are dose-dependent and can be accentuated following rapid bolus administration and in patients with compromised cardiovascular function. The adverse hemodynamic profile of propofol administration can be prevented by the administration of calcium chloride [194]. Additional cardiovascular effects may be caused by augmentation of central vagal tone leading to bradycardia, conduction disturbances, and asystole [195–197]. These effects are more likely with the concomitant administration of other medications known to alter cardiac chronotropic function including fentanyl or succinylcholine.

Various neurological manifestations have been reported with the administration of propofol including opisthotonic posturing, myoclonic movements (especially in children), and movements that may resemble seizure-like activity [198–200]. Myoclonus, opisthotonic posturing, and other movements with propofol have been attributed to propofol's antagonism at glycine receptors in subcortical structures. To date, there is no formal evidence linking propofol with seizures [201]. Propofol remains an effective agent for the termination of refractory status epilepticus and remains in various published algorithms regarding recommendations for its treatment [202, 203].

Despite its potential benefits in the ICU setting and its efficacy for providing sedation during mechanical ventilation, the routine use of propofol is not recommended and, in fact, is considered contraindicated by many authorities because of the potential for the development of what has been termed the "Propofol Infusion Syndrome." First described in 1992 by Parke et al., the disorder includes metabolic acidosis, bradycardia, dysrhythmias, rhabdomyolysis, and fatal cardiac failure [204–206]. Eighteen children in the ICU setting with suspected propofol infusion syndrome were reviewed in a report by Bray [207]. The risk factors in the cohort for the development of the syndrome included propofol administration for ≥48 h or an infusion rate ≥4 mg/kg/h. However, not all patients meeting these risk factor criteria developed problems, suggesting that comorbid diseases or a genetic predisposition may be responsible for the development of the Propofol Infusion Syndrome. Additionally, 13 of the 18 patients were ≤4 years of age while only one was ≥10 years of age. Subsequent to the initial reports and the review of Bray et al., the syndrome has been reported in older patients including a 17-year-old adolescent and adults [208–210]. In addition to the metabolic acidosis and cardiovascular manifestations, additional clinical findings have included lipemic serum, hepatomegaly, rhabdomyolysis, and hyperkalemia.

The suggested treatment for Propofol Infusion Syndrome includes the immediate discontinuation of the propofol combined with symptomatic treatment of cardiovascular dysfunction and acidosis. Reports in animals and humans suggest that this syndrome is related to a disruption in mitochondrial function [211–213]. Anecdotal evidence suggests that hemodialysis may be helpful as a therapeutic tool by removing a yet undiagnosed metabolite or toxin [212, 213].

Despite these concerns, it appears that the contention that we should abandon the use of propofol for sedation during mechanical ventilation in the PICU setting has not been universally embraced. Although propofol has been used safely and effectively for sedation in small cohorts of PICU patients [214–218], the decision to use propofol should be considered in context of the "Dear Healthcare Provider" letter issued in March 2001 by AstraZeneca (Wilmington, DE), the manufacturers of Diprivan®, one of the commercially available propofol preparations [219]. The letter summarizes the results of a prospective clinical trial which compared propofol (a 1 or 2% solution) to other agents used for PICU sedation. There were 12 (11%) deaths in the 2% propofol group, 9 deaths (8%) in the 1% propofol group, and 4 deaths (4%) in the standard sedation group. Although subsequent review did not show a specific pattern to the deaths, there was enough concern that the company issued a letter stating: "propofol is currently not approved for sedation in PICU patients in the United States and should not be used for this purpose." In many centers, these concerns have eliminated the prolonged use of propofol for sedation in the PICU.

In specific clinical scenarios, propofol is still used as a therapeutic tool in the treatment of refractory status epilepticus or increased ICP. In such cases, intermittent analysis of acid–base status and creatinine phosphokinase is suggested. If a base deficit is noted with an increasing serum lactate, immediate discontinuation of the propofol is recommended. Additionally, the short-term administration of propofol (6–12 h) is still used in many centers to transition from other agents such as fentanyl and midazolam to allow for more rapid awakening for tracheal extubation. Short-term propofol infusions may also have a role in the arena of procedural sedation as a means of providing sedation during nonpainful invasive procedures such as radiologic imaging. Although rare, when such procedures are long, concern has also been expressed regarding the potential development of the Propofol Infusion Syndrome [220].

Additional concerns with propofol regarding its use for procedural sedation in spontaneously ventilating patients include a relatively high incidence of respiratory effects including hypoventilation, upper airway obstruction and progression to general anesthesia and apnea, many of which required bag-mask ventilation or repositioning of the airway [221, 222].

As propofol is delivered in a lipid emulsion, there may be allergic reactions, pain on injection, and elevated triglyceride levels or hypercapnia with prolonged infusions [223–225]. Cross-reactivity may occur in patients with allergies to egg, egg products, soy beans, or soy products. A propofol infusion of 2 mg/kg/h provides approximately 0.5 g/kg/day of fat. To limit the impact of the lipid component, a 2% solution of propofol (twice the amount of propofol with the same amount of lipid per mL as the 1% solution) has undergone clinical evaluations [226–229]. Given the concerns regarding the lipid component, its fat content should be considered into daily caloric requirements if prolonged infusions are used.

Pain with the injection of propofol remains a significant complaint especially when small veins on the dorsum of the hands or feet are used. Variable success in decreasing the incidence of pain has been reported with various maneuvers including the preadministration of lidocaine, mixing the lidocaine and propofol in a single solution, mixing the propofol with thiopental, diluting the concentration of the propofol, cooling it prior to bolus administration, or the administration of a small dose of ketamine (0.5 mg/kg) prior to the administration of propofol [230–234].

One final issue with the lipid component of propofol is its potential to serve as a viable growth media for bacteria with reports of bacteremia and postoperative wound infections linked to extrinsically contaminated propofol [235, 236]. Various preservatives are used in the currently available propofol solutions including disodium EDTA or sodium metabisulfite. In clinical practice, there may be subtle yet clinically significant differences in these preparations, including differential effects on airway reactivity which have already been discussed in this chapter [192, 193]. Trissel et al. have provided preliminary information that the compatibility of various medications is different with the two propofol preparations [237]. This is an important issue for pediatric

patients in whom intravenous access may be limited. The literature contains contrasting information regarding the anesthetic potency of the two preparations [238–239]. A theoretical disadvantage of disodium EDTA is the chelation and depletion from the body of essential trace minerals such as zinc. Although there are no formal studies to demonstrate that this is a problem, concerns related to this issue are outlined in the manufacturer's package insert.

Barbiturates

The barbiturates were first synthesized in 1864 by von Baeyer. Thiopental, a short-acting barbiturate was first administered for clinical use in 1934. This class of anesthetic agent can be classified according to their chemical structure or their duration of activity. Short-acting agents such as methohexital, thiopental, and thiamylal have a clinical duration of action of 5–10 min and are used most commonly as a single bolus dose for the induction of anesthesia. When a more prolonged effect is needed, a continuous infusion may be used to maintain constant plasma levels. Long-acting agents with half-lives of 6–12 h include pentobarbital and phenobarbital. The clinical effects of the short-acting agents dissipate rapidly related to their redistribution, although their hepatic metabolism may take hours. However, when this is done, the offset time will also be markedly prolonged and dependent on the duration of the infusion.

In the PICU setting, the barbiturates are occasionally used by continuous infusion for sedation during mechanical ventilation (see below) although their more common use is based on their beneficial physiologic and therapeutic effects as anticonvulsants or to decrease ICP in patients with traumatic brain injury [240–245].

The ultra-short-acting barbiturates (thiopental and thiamylal) are used clinically in a 2.5% solution with a pH 10.5. The high pH results in a bacteriostatic solution limiting concerns of bacterial contamination as well as limiting the pain that may occur with intravenous injection. However, the pH of 10.5 leads to incompatibilities with other medications and parenteral alimentation solutions, thereby necessitating a separate infusion site if a continuous infusion is used. Of particular note is the potential for the barbiturates to form precipitates when administered with drugs such as rocuronium, mandating flushing the line during the rapid administration of medications during maneuvers such as rapid sequence intubation (to avoid loss of intravenous access during critical moments). Local erythema, thrombophlebitis, or skin sloughing may occur with subcutaneous infiltration. The barbiturates possess no analgesic properties and therefore should be used with an opioid in situations requiring analgesia.

The barbiturates' place in ICU sedation appears to be an alternative or second-line agent when primary agents, either alone or in combination, fail to provide adequate sedation or result in untoward side effects [246]. There are a limited number of reports regarding the use of pentobarbital infusions for sedation in the PICU setting. A retrospective report described the use of pentobarbital for sedation during mechanical ventilation of 50 infants and children, ranging in age from 1 month to 14 years [247]. Pentobarbital was administered for a median duration of 4 days (range 2–37 days) at a median dose of 2 mg/kg/h (range 1–6 mg/kg/h). The cohort included seven non-neonatal ECMO patients in whom pentobarbital provided effective sedation. Tolerance was noted with the administration of pentobarbital. In the 14 patients who received pentobarbital for ≥5 days, the dose requirements increased from 1.2 mg/kg/h on day #1 to 3.4 mg/kg/h on day #5. No significant adverse effects related to pentobarbital were noted. Six of the 36 patients who had received pentobarbital for more than 4 days manifested signs and symptoms of withdrawal.

Yanay et al. reported their retrospective experience with pentobarbital sedation for eight PICU patients [248]. Although pentobarbital provided effective sedation and allowed the discontinuation of neuromuscular blocking agents, they noted a relatively high incidence of adverse effects including blood pressure instability (25%), oversedation (12.5%), and neurologic sequelae (12.5%) including withdrawal phenomena. These adverse effects led to discontinuation of the drug in 25% of their patients.

In addition to their role for therapeutic agents or perhaps for the provision of sedation during mechanical ventilation, there are several reports outlining the use of various barbiturates for procedural sedation. As they have no intrinsic analgesic properties, the barbiturates are used most commonly for sedation during nonpainful procedures.

The short-acting oxybarbiturate, methohexital, has been used extensively via both oral and PR route as a sedative for CT or MR imaging with success rates of up to 80–85% [249]. The standard dose per rectum is 20–30 mg/kg, which produces a rapid onset of sleep (6–10 min) with recovery to baseline status within 1.5–2 h. Adverse effects are uncommon with mild respiratory depression responsive to repositioning or the administration of supplemental oxygen occurring in up to 4% of patients. The duration of action with intravenous use (0.75–1.0 mg/kg) is approximately 10 min, making the drug attractive for short procedures such as CT imaging. However, the incidence of respiratory depression is greater with the intravenous route of administration, which may limit its usefulness. Unlike the other barbiturates, methohexital may activate the EEG and has been reported to precipitate seizures in patients with underlying seizure disorders.

Although used most commonly by the intravenous route for the induction of anesthesia, thiopental has also been used as a rectal agent for sedation for radiologic procedures in doses of 25–50 mg/kg [250, 251]. When compared with methohexital, the depth of sedation achieved and reported success rates were somewhat higher (>90%). The onset of action is slightly longer (15–30 min) with a similar duration of action (60–90 min) compared to methohexital.

Pentobarbital has an intermediate duration of action and remains a popular choice for intravenous sedation during radiologic procedures such as MR imaging where sedation times may approach 60–90 min. Multiple delivery options are available including the IV, IM, and enteral routes, although IV administration remains the most commonly used route. Pentobarbital is administered in increments of 1–2 mg/kg every 3–5 min until sleep is induced (average total dose 4–5 mg/kg) [252, 253]. The average duration of sleep after a single intravenous dose is 60–90 min, which is adequate to perform most routine MRI evaluations. Respiratory depression and hypotension may occur, especially with rapid intravenous administration. Disadvantages with pentobarbital include prolonged recovery times (2–4 h) and emergence issues including agitation.

Opioids

Although generally used for analgesia, opioids also possess sedative properties; especially those with agonistic effects at the κ opioid receptor [254]. Therefore, these agents may be effective for providing sedation during mechanical ventilation and remain second to the benzodiazepines as the most commonly used agents in the PICU setting. Although the opioids provide analgesia, amnesia is not ensured. Therefore, additional agents are required in situations which demand amnesia such as the patient who is receiving a neuromuscular blocking agent. In patients with altered myocardial function or at risk for pulmonary hypertension (such as an infant with a large preoperative left-to-right shunt), the synthetic opioids have been shown to provide cardiovascular stability, beneficial effects on pulmonary vascular resistance, and blunting of sympathetic stress response. Due to their prompt redistribution and resultant short plasma half-lives following bolus administration, the synthetic opioids are generally administered by a continuous infusion to maintain plasma concentrations adequate to provide sedation and analgesia.

The synthetic opioids that are currently in common clinical use include fentanyl, sufentanil, alfentanil, and remifentanil. Fentanyl is the least expensive of the synthetic opioids and the one with which there is the most clinical experience in the PICU setting. Fentanyl, sufentanil, and alfentanil are dependent on hepatic metabolism. Although these agents are short acting when administered as a single bolus dose, they also have a context-sensitive half-life, so that the duration of their effect is prolonged when they are administered over an extended period of time.

Unlike the other opioids which undergo hepatic metabolism, remifentanil is metabolized by nonspecific esterases in the plasma. It has a clinical half-life of 5–10 min and a brief duration of effect even following 12–24 h of continuous infusion [255]. These pharmacokinetic parameters hold true even in the neonatal population, making remifentanil the only opioid whose pharmacokinetics is not altered by gestational or chronologic age [256]. Given these properties, it is a potentially useful agent for providing a deep level of sedation and yet allowing for rapid awakening with discontinuation of the infusion even in the neonatal population. To date, there remains limited experience with its use in the ICU population.

Cavaliere et al. evaluated the efficacy of a remifentanil infusion in doses starting at 0.02 μg/kg/min and increasing up to 0.25 μg/kg/min, in providing sedation during mechanical ventilation in a cohort of ten adult ICU patients [257]. Although sedation, assessed by clinical sedation scales, was adequate in the ten patients, the maximum infusion rate was achieved in only 4 of the 10 patients due to the occurrence of adverse effects including hypotension and bradycardia at infusion rates ≥0.15 μg/kg/min. Hypoventilation was noted at infusion rates as low as 0.1 μg/kg/min.

In a prospective, randomized trial, adults requiring mechanical ventilation received either a morphine infusion at 0.75 μg/kg/min or a remifentanil infusion at 0.15 μg/kg/min [258]. The percentage of optimal sedation hours was significantly greater with remifentanil. There was no difference in the incidence of adverse effects.

To date, there are only anecdotal reports regarding the use of remifentanil for sedation during mechanical ventilation in the PICU population [259].

An issue that needs further investigation prior to its widespread application in the ICU setting is the rapid development of tolerance. In adult volunteers, tolerance to remifentanil may develop after only 60–90 min [260]. This has translated into the need to escalate doses rapidly when remifentanil is used for ICU sedation [259–261]. Although tolerance may limit prolonged remifentanil infusions, there remains interest in the use of remifentanil in the arena of procedural sedation given that its effects dissipate rapidly when the infusion is discontinued [262–264]. Remifentanil has been combined with midazolam or propofol for painful, invasive procedures such as bronchoscopy or for fiberoptic intubation of the trachea [263].

Two additional issues relevant to the synthetic opioids are potential effects on ICP and the risks of chest wall rigidity. Anecdotal reports suggested the potential for the synthetic opioids to increase ICP and decrease CPP in adults with altered intracranial compliance [265]. Rather than a direct effect, the mechanism responsible for the ICP increase has been shown to be a reflex cerebral vasodilation in response to the decrease in mean arterial pressure or CPP [266].

A second adverse effect specific to the synthetic opioids is chest wall and laryngeal rigidity [267, 268]. These effects are related to the dose and the rate of administration. They are centrally mediated responses which can interfere with respiratory function. The incidence can be decreased by premedication with the α_2-adrenergic agonists, reversed with naloxone, and interrupted with neuromuscular blocking agents. Although rare, its occurrence should be considered if respiratory dysfunction is noted following the use of synthetic opioids.

Given issues with the rapid development of tolerance following the use of the synthetic opioids, morphine has regained popularity for sedation and analgesia during mechanical ventilation in the PICU setting. Given that morphine has agonistic effects at both the mu and the kappa opioid receptor, it provides not only analgesia via the mu receptor but also sedation via the kappa receptor. Cardiovascular effects include dilation of the venous capacitance system with a decrease in preload which may result in a modest decrease in blood pressure, especially in patients with decreased intravascular volume or comorbid cardiac diseases.

When used by continuous infusion for sedation during mechanical ventilation in neonates, morphine has been shown to have no effect on intelligence, motor function, or behavior [269]. In infants, morphine infusions of 10–30 μg/kg/h provided effective analgesia and sedation during

mechanical ventilation after surgery for congenital heart disease without impairing the ability to wean mechanical ventilatory support [270]. Morphine infusions blunt the sympathetic response and reduce epinephrine levels in neonates requiring endotracheal intubation and mechanical ventilation for hyaline membrane disease [271].

In a cohort of infants requiring sedation and analgesia during ECMO (mean duration of ECMO 4–5 days), morphine and fentanyl provided equivalent levels of sedation while decreasing the need for supplemental bolus doses of opioid [272]. Infants receiving morphine had a lower incidence of withdrawal (13 of 27 with fentanyl vs. 1 of 11 with morphine, $p<0.01$) and were hospitalized for fewer days after ECMO (31.1 ± 14 vs. 21.5 ± 7.0 days, $p=0.01$).

Although administered most commonly via the intravenous route, rare circumstances such as limited intravenous access or drug incompatibilities may occur which preclude intravenous administration in the PICU setting. In such situations, the subcutaneous administration of opioids is feasible [72, 273–276].

As with all of the previously described agents, opioids may have adverse effects on respiratory function with the potential for hypoventilation or apnea. However, an effect which appears to be relatively specific to the opioids is their potential impact on immune function [277–279]. Opioid receptors have been found on immune cells which participate in the inflammatory response and various host defenses [278, 279]. Although there are no studies directly linking these effects to adverse clinical outcomes, additional studies are needed to define these effects, their mechanisms, and most importantly their impact on the PICU patient.

Phenothiazines and butyrophenones

The phenothiazines and butyrophenones are classified as the "major tranquilizers." The majority of their clinical use is in the treatment of psychiatric disturbances or as antiemetics in various clinical scenarios. Of the several agents available, haloperidol is the agent that has been used most frequently for the sedation of adults in the ICU setting. Haloperidol acts through central dopamine receptors. With intravenous administration, its onset of action is within 10–20 min with a duration of action of 12–24 h given its long elimination half-life of 18–26 h [280]. Although not formally approved by the FDA for intravenous administration, there is an abundance of clinical experience with its use by this route [281].

Riker et al. reported their experience with the continuous infusion of haloperidol in doses ranging from 3 to 25 mg/h for sedation in eight adult ICU patients [282]. They proposed various benefits of haloperidol including a rapid onset, minimal respiratory depression, and lack of active metabolites.

A retrospective report regarding haloperidol use in a cohort of 989 adult patients, who required mechanical ventilation for more than 48 h, reported not only efficacy in controlling agitation and delirium but also a lower overall in-hospital mortality in patients who received haloperidol [283].

Experience with haloperidol in the PICU population remains anecdotal. Harrison et al. reported their experience with haloperidol, administered by intermittent bolus dosing to five critically ill children (9 months to 16 years) who had become difficult to sedate despite escalating doses of benzodiazepines and opioids [284]. Haloperidol's efficacy was demonstrated by a reduction of opioid and benzodiazepine requirements, decreased need for supplemental doses of sedative agents, decreased use of neuromuscular blocking agents, and improved clinical sedation. One patient developed a dystonic reaction which resolved in 36 h without therapy as the haloperidol had already been discontinued.

Potential adverse effects associated with the butyrophenones and phenothiazines include hypotension related to peripheral α-adrenergic blockade, dystonic and extrapyramidal effects, lowering of the seizure threshold, the neuroleptic malignant syndrome, and cardiac arrhythmias including *torsades de pointes* due to effects on cardiac repolarization [282]. The potential for cardiac dysrhythmias due to alterations in repolarization may be exacerbated in critically ill patients with altered sympathetic function related to fever, pain, or the stresses of an acute illness.

Similar issues may occur with other drugs of this class including droperidol [285].

Through a black box warning issued by the United States Food and Drug Administration, concern has been expressed regarding the potential association of droperidol and postoperative cardiac events including *torsades de pointes* in adult patients [286]. Prolonged postoperative ECG monitoring is suggested in patients treated with droperidol during the perioperative period.

Alpha$_2$-adrenergic agonists

Although used initially for clinical effects such as the control of blood pressure, the α_2-adrenergic agonists including clonidine and dexmedetomidine may also have a role in the PICU patient for the provision of sedation during mechanical ventilation, reduction of opioid requirements, the control of pain of various etiologies, and provision of sedation during noninvasive procedures. The physiologic effects of these agents are mediated via stimulation of postsynaptic α_2-adrenergic receptors [287–290]. Activation of receptors in the medullary vasomotor center reduces norepinephrine turnover and decreases central sympathetic outflow resulting in alterations in sympathetic function with decreased heart rate and blood pressure.

Additional effects result from the central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus cereleus in the brainstem. The latter effect plays a prominent role in the sedation and anxiolysis produced by these agents as decreased noradrenergic output from the locus cereleus allows for increased firing of inhibitory neurons including the GABA system, resulting in sedation and anxiolysis [291]. This effect has been shown to be similar to that which occurs during non-REM sleep [292, 293]. The lack of non-REM sleep with the use of other sedative agents including propofol, benzodiazepines, and barbiturates is one of the factors that may result in delirium in adult ICU patients. The α_2-adrenergic agonists also potentiate the analgesic effects of opioids by regulating substance P release within the central nervous system.

Clonidine has been used as a premedicant in the operating room, for caudal and epidural analgesia, as an adjunct to opioid-induced analgesia during the postoperative period, and even for ICU sedation [294–298]. Although initially available only as a tablet, clonidine is now available as a transdermal patch and as a preparation for neuraxial administration. The latter has been administered intravenously in various clinical scenarios.

In an open label evaluation in children in the PICU setting, a continuous clonidine infusion starting at 1 μg/kg/min was added to a continuous midazolam infusion of 1 μg/kg/min [298]. No significant changes in heart rate, blood pressure, or cardiac index were noted. In 2 of the 20 patients, the clonidine infusion was increased to 2 μg/kg/h. The clonidine infusion provided adequate sedation for 602 of the 672 study hours with no sedation failures.

Arenas-Lopez et al. reported their experience with the addition of enteral clonidine (3–5 μg/kg every 8 h) as an adjunct to intermittent doses of morphine and lorazepam for sedation during mechanical ventilation in 14 children [299]. Adequate sedation was achieved during 82% of the study period with an overall decrease in the requirements for both lorazepam and morphine. No adverse effects were noted.

More recently, dexmedetomidine has been released for clinical use and sedation [300–302]. Like clonidine, it is a centrally acting, α_2-adrenergic agonist and exhibits the same physiologic effects. However, it possesses an affinity 8 times that of clonidine for the α_2-adrenergic receptor, a differential α_1 to α_2 agonism of 1:1,600, and a half-life of 2–3 h thereby allowing its titration by intravenous administration.

In healthy adult volunteers, the pharmacokinetic profile of dexmedetomidine includes a rapid distribution phase with a distribution half-life of approximately 6 min, an elimination half-life of 2 h. Dexmedetomidine exhibits linear kinetics, is 94% protein bound, and undergoes hepatic metabolism with minimal unchanged drug excreted in the urine and feces. Given its dependence on hepatic metabolism, dose adjustments are necessary in patients with altered hepatic function.

To date, there is only one prospective trial evaluating dexmedetomidine for sedation during mechanical ventilation in pediatric-aged patients

[303]. Efficacy was evaluated using the Ramsay Scale and by comparing the requirements for supplemental morphine. Dexmedetomidine at 0.25 μg/kg/h provided sedation that was equivalent to midazolam at 0.22 mg/kg/h. Dexmedetomidine at 0.5 μg/kg/h was more effective than midazolam as demonstrated by a decreased need for supplemental morphine and a decrease in the number of Ramsay scores of 1 exhibited by the patients. Dexmedetomidine was somewhat less effective in patients ≤12 months of age as 5 of the 6 patients who exhibited a Ramsay score of 1 during dexmedetomidine were less than 12 months of age. The only adverse effect was bradycardia in one patient receiving dexmedetomidine who was also receiving digoxin [304].

In addition to its use for sedation during mechanical ventilation, other applications of dexmedetomidine have included procedural sedation, prevention of shivering, and treatment of iatrogenic opioid and benzodiazepine withdrawal following prolonged use in the ICU setting [300].

Koroglu et al. randomized 80 children (1–7 years of age) to dexmedetomidine or midazolam during MR imaging [305]. Dexmedetomidine was administered as a loading dose of 1 μg/kg over 10 min followed by an infusion of 0.5 μg/kg/h while midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 μg/kg/h. The quality of sedation was better and the need for rescue sedation was less (8 of 40 vs. 32 of 40) with dexmedetomidine compared to midazolam. Similar efficacy was reported in an open label trial of dexmedetomidine for sedation during MR imaging in 48 pediatric patients ranging in age from 5 months to 16 years [306]. Fifteen patients had failed chloral hydrate and/or midazolam and 33 patients received dexmedetomidine as the primary agent. The mean loading dose of dexmedetomidine to initiate sedation was 0.92 ± 0.36 μg/kg. This was followed by an infusion of 0.69 ± 0.32 μg/kg/h. Effective sedation was achieved in all patients and the scan was completed without other agents. Recovery time was longer in patients who had received other agents prior to dexmedetomidine than in those who received dexmedetomidine as a primary agent (117 ± 41 vs. 69 ± 34 min).

A second study by Koroglu et al. randomized 60 children to dexmedetomidine or propofol during MR imaging [307]. Although both of the agents were equally effective in providing sedation, propofol provided shorter induction times, recovery times, and discharge times. However, adverse effects including hypotension and oxygen desaturation were more common with propofol. Oxygen desaturation requiring intervention including a chin lift, discontinuation of the infusion, or supplemental oxygen occurred in 4 of 30 children receiving propofol vs. 0 of 30 receiving dexmedetomidine.

In a retrospective review of their Quality Assurance database, Mason et al. used escalating doses of dexmedetomidine for sedation in 62 children during radiological imaging [308]. Dexmedetomidine was administered as a loading dose of 2 μg/kg over 10 min and repeated to achieve effective sedation after which an infusion was started at 1 μg/kg/h. The mean loading dose was 2.2 μg/kg with 52 patients requiring only the initial dose of 2 μg/kg. The time to achieve sedation ranged from 6 to 20 min. Sinus arrhythmias were noted in ten patients (16%). Heart rate and blood pressure decreased in all patients; however, no treatment was necessary and no hemodynamic value was less than the fifth percentile for age. No changes were observed in the $ETCO_2$ and no patient developed oxygen desaturation while breathing room air.

Given its limited analgesic effects, dexmedetomidine may not be the ideal agent when used alone for painful procedures. However, anecdotal experience suggests that a combination of dexmedetomidine with ketamine may be effective in such scenarios [309–312].

With the prolonged administration of any agent for sedation or analgesia, tolerance occurs and withdrawal may be seen if the medication is abruptly discontinued. Regardless of the agent or agents responsible, the potential role of dexmedetomidine in treating such problems is supported by animal studies [313–316], case reports in adults and children [317–321], and one retrospective case series in infants [322]. The latter study was a retrospective review of seven infants (3 to 24 months). Sedation had been provided during

mechanical ventilation with a continuous infusion of fentanyl supplemented with intermittent doses of midazolam. With discontinuation of the fentanyl and midazolam, withdrawal occurred. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg/h followed by an infusion of 0.5 μg/kg/h. The loading dose was repeated and the infusion increased to 0.7 μg/kg/h in the two patients who had received the highest doses of fentanyl (8.5 ± 0.7 vs. 4.6 ± 0.5 μg/kg/h, $p < 0.0005$). Withdrawal was successfully controlled.

As with all of the medications discussed in this chapter, dexmedetomidine has been reported to effect cardiovascular function [302, 323–327]. Adverse hemodynamic effects include hypotension (mean arterial pressure ≤60 mmHg or a greater than 30% decrease from baseline) or bradycardia (heart rate ≤50 beats/min) [302]. Talke et al. evaluated the efficacy of dexmedetomidine infusion in a cohort of 41 adults during vascular surgery [324]. There was a lower heart rate, less tachycardia, and decreased norepinephrine levels during emergence from anesthesia in patients receiving dexmedetomidine.

Electrophysiologic effects were also reported in an intraoperative study by Peden et al. [325]. Two patients who received dexmedetomidine experienced brief episodes of sinus arrest following laryngoscopy and propofol administration. These findings suggest that specific procedures (laryngoscopy), techniques (hypothermia to control ICP or for neuroprotection), and medications (propofol, fentanyl, digoxin) may potentiate the vagotonic effects of dexmedetomidine.

Given these effects on cardiac conduction, it has been suggested that dexmedetomidine may not be a desirable agent for sedation in the cardiac catheterization suite when electrophysiologic studies are planned [326]. However, other authors have demonstrated that these negative chronotropic properties may be used as a therapeutic tool in infants and children who develop tachyarrhythmias following surgery for congenital heart disease [327].

Data in animal and human studies demonstrate beneficial effects on cerebral dynamics including a decrease in CBF and ICP [328, 329]. However, given the potential effects on mean arterial pressure, decreases in CPP may occur [330]. As with, the barbiturates, propofol and the inhalational anesthetic agents, animal data suggest that dexmedetomidine may provide some degree of cerebral protection during periods of global or regional cerebral ischemia [331–333]. The data in animal studies regarding its effects on the seizure threshold are mixed depending on the provocative agent and the type of animal studied, with two studies suggesting a lowering of the seizure threshold and two suggesting an anticonvulsant effect [334–337].

Chloral hydrate

Chloral hydrate, first synthesized in 1832, remains a commonly used agent for procedural sedation [338]. Its popularity results from several factors including its ease of administration by either oral or rectal route, healthcare providers' familiarity with it, and misconceptions regarding its margin of safety. Following oral or rectal administration, chloral hydrate is rapidly absorbed. It undergoes hepatic metabolism to its active metabolite, trichloroethanol (TCE). Although generally effective as a one-time agent for nonpainful radiologic procedures, repeated dosing in the PICU setting leads to excessive and prolonged CNS depression due to a variable half-life ranging from 9 to 40 h as well as the accumulation of active metabolites [339]. These issues have resulted in recommendations against such practices from the AAP [340].

Chloral hydrate is relatively contraindicated in neonates given its competition with bilirubin for protein binding sites. Additionally, the active metabolite, TCE, is related to the halogenated hydrocarbons and may cause ventricular arrhythmias especially in patients at risk for such problems (tricyclic antidepressant ingestions or underlying arrhythmia) [341, 342]. Given these issues, chloral hydrate has a limited role in sedation in the PICU setting; however, it may still have a place for sedation during nonpainful radiologic imaging [343]. Used for this purpose, doses of 75–100 mg/kg (maximum 2 g) can be administered by mouth or per rectum.

Tolerance, Physical Dependency, and Withdrawal

Over the past several years, data demonstrating the potential deleterious physiologic effects of untreated pain combined with ongoing humanitarian concerns have led to the increased use of sedative and analgesic agents. These initiatives have led to new consequences including physical dependency, tolerance, and withdrawal that require definition and effective treatment strategies. An appropriate place to begin the development of an effective approach to the patient with tolerance and physical dependency is a consensus on definitions of these terms [343]. Tolerance is a decrease in a drug's effect over time or the need to increase the dose to achieve the same effect. Tolerance is related to changes at or distal to the receptor, generally at the cellular level. Some authorities have divided tolerance into various subcategories including innate tolerance referring to a genetically predetermined lack of sensitivity to a drug, pharmacokinetic or dispositional tolerance referring to changes in a drug's effect because of alterations in distribution or metabolism, learned tolerance or a reduction in a drug's effect as a result of learned or compensatory mechanisms (learning to walk a straight line while intoxicated by repeated practice at the task), and pharmacodynamic tolerance [343]. With pharmacodynamic tolerance, although the plasma concentration of the drug remains constant, there is a decreased effect. For the purpose of this discussion, the latter phenomenon will be referred to as tolerance as the other issues are not as relevant when considering the PICU patient.

Withdrawal includes the physical signs and symptoms that manifest when the administration of a sedative or analgesic agent is abruptly discontinued in a patient who is physically tolerant. The symptomatology of withdrawal varies from patient to patient and may be affected by several factors including the agent involved, the patient's age, cognitive state, and associated medical conditions.

Physiologic (physical) dependence is the need to continue a sedative or analgesic agent to prevent withdrawal. Psychological dependence is the need for a substance because of its euphoric effects. Addiction is a complex pattern of behaviors characterized by the repetitive, compulsive use of a substance, antisocial or criminal behavior to obtain the drug, and a high incidence of relapse after treatment. Psychological dependency and addiction are extremely rare after the appropriate use of sedative or analgesic agents to treat pain or to relieve anxiety in the PICU setting.

The problems of opioid dependency and withdrawal in neonates and infants were first encountered in the 1970s and 1980s in infants of drug-addicted mothers [344–346]. Despite the difference in the origin of the problem, these studies provided valuable information for dealing with today's PICU population. The studies from the 1970s and 1980s have provided various pharmacologic treatment regimens as well as scoring systems that may be used to grade the severity of withdrawal and to evaluate the efficacy of the treatment regimens. Arnold et al. were among the first to recognize the problems of dependency and withdrawal after prolonged opioid administration in the PICU population [347].

In a retrospective review of 37 neonates who required extracorporeal membrane oxygenation (ECMO) for respiratory failure and who had received intravenous fentanyl for sedation, they sought to identify the signs and symptoms of the neonatal abstinence syndrome (NAS) and risk factors for its occurrence. Fentanyl infusion requirements to achieve the desired level of sedation increased from 11.6 ± 6.9 μg/kg/h on day 1 to 52.5 ± 19.4 μg/kg/h on day 8. By measuring plasma fentanyl levels, they were able to demonstrate that the tolerance was pharmacodynamic and not pharmacokinetic (related to increased metabolism of the opioid). NAS was related to the total fentanyl dose and the duration of the infusion. A cumulative fentanyl dose ≥1.6 mg/kg and an ECMO duration ≥5 days were risk factors for the development of NAS (odds ratio of 7 and 13.9, respectively).

In a cohort of eight infants placed on ECMO, fentanyl infusion requirements increased from 9.2 ± 1.9 μg/kg/h on day 1 to 21.9 ± 4.5 μg/kg/h on day 6 [348]. As in their previous study, they noted an increase in the plasma fentanyl concentration from 3.1 ± 1.1 ng/mL on day 1 to 13.9 ± 3.2 ng/mL on day 6.

Subsequent reports demonstrated withdrawal from other agents used for prolonged sedation in the PICU patient including benzodiazepines, barbiturates, propofol, and even the inhalational anesthetic agents. Sury et al. described benzodiazepine withdrawal in three children, who were 4, 11, and 12 years of age, after prolonged sedation with a continuous infusion of midazolam [350]. The patients had received midazolam for 7, 14, and 17 days at mean infusion rates of 0.17, 0.22, and 0.56 mg/kg/h. The midazolam infusions were stopped without tapering the infusion rate and within 24 h, withdrawal symptoms were noted including visual hallucinations, combative behavior, and seizures. The problems resolved once a benzodiazepine was administered.

Van Engelen et al. reported similar problems after the prolonged administration of midazolam to two pediatric patients [351]. The midazolam infusion rates reached maximum values of 0.14 and 0.57 mg/kg/h with durations of infusion of 12 and 29 days. After discontinuation of the midazolam infusion, both patients manifested withdrawal symptoms that included agitation, tachycardia, hyperpyrexia, and vomiting. Symptoms disappeared with reinstitution of the midazolam infusion.

Fonsmark et al. evaluated 40 children who received sedation during mechanical ventilation. Sedation was provided by midazolam, pentobarbital, or a combination of the two [352]. Withdrawal symptoms occurred in 14 of 40 patients (35%). A cumulative midazolam dose ≥60 mg/kg or a cumulative pentobarbital dose ≥25 mg/kg was associated with withdrawal, irrespective of the duration of infusion.

Other anecdotal reports have noted withdrawal following the use of pentobarbital for sedation in the PICU population [353]. The potential for the development of tolerance to barbiturates is further supported by animal studies demonstrating the rapid development of tolerance after repeated administration and an increased susceptibility to pentylenetetrazol-induced seizures as a manifestation of barbiturate withdrawal [354, 355].

Despite the concerns outlined above regarding propofol, it is still used for sedation during mechanical ventilation. In a retrospective review of acute withdrawal after prolonged sedation with propofol in the adult ICU patient, there was a correlation of the incidence of withdrawal behavior in patients with both the use of propofol as part of the sedation regimen and the dose administered [356]. Anecdotal evidence supports the occurrence of propofol withdrawal in a 10-month-old girl who required mechanical ventilatory support for 2 weeks after an inhalation smoke injury [357]. Propofol was administered for 2 weeks during mechanical ventilation. When the drug was discontinued, the patient exhibited "generalized twitching and jitteriness." No treatment was administered, and the symptoms subsided over a 3-day period.

One of the more novel approaches for sedation during mechanical ventilation is the administration of inhalational anesthetic agents, such as isoflurane. Arnold et al. reported their experience with the use of isoflurane to ten pediatric patients for sedation during mechanical ventilation (see above) [58]. During the administration of isoflurane, the opioid and benzodiazepine infusions were gradually tapered and discontinued. Although the inhalational agent proved effective in providing sedation, agitation and nonpurposeful movements occurred in 5 of the 10 patients within 2 h of discontinuation of isoflurane. These five patients had received more than 70 MAC-hours of isoflurane.

Arnold et al. subsequently reported tolerance and withdrawal phenomena after the prolonged administration of isoflurane to a 4-year-old boy for sedation during mechanical ventilation [358]. After 19 days of administration, with an end-tidal isoflurane concentration of 0.8–1.2%, the patient was awake and able to follow commands. After 32 days of administration, mechanical ventilation and the isoflurane were discontinued. Shortly after discontinuing the isoflurane, the patient developed agitation, diaphoresis, tachycardia, hypertension, and profuse diarrhea. The symptoms were eventually controlled with pentobarbital and midazolam infusions. Hughes et al. reported hallucinations and seizures after the prolonged administration of isoflurane for sedation to a 7-year-old boy [359].

Clinical signs and symptoms of withdrawal

The development of strategies to provide effective treatment of physical dependency and related problems requires the accurate identification and recognition of withdrawal symptoms. Ongoing or associated conditions that can manifest similar clinical signs and symptoms as withdrawal must be investigated and ruled out before concluding that the patient's symptoms are the result of withdrawal. In the PICU patient, these associated conditions may include central nervous system insults or infections, ICU psychosis, delirium, metabolic abnormalities, hypoxia, hypercarbia, and cerebral hypoperfusion from alterations in cardiac output or cerebral vascular disease.

Although many of the signs and symptoms of withdrawal are the same regardless of the agent, there may be subtle differences depending on the specific agent. The time to the onset of withdrawal symptoms varies depending on the half-life of the agent and the half-life of active metabolites, which may be several times longer than the parent compound. In general, the signs and symptoms of withdrawal from sedative and analgesic agents include signs and symptoms related to the CNS, the gastrointestinal tract, and the sympathetic nervous system. CNS manifestations are generally those of increased irritability including decreased sleep, tremulousness, hyperactive deep tendon reflexes, clonus, inability to concentrate, frequent yawning, sneezing, delirium, and hypertonicity. In neonates and infants, additional signs of central nervous system stimulation include a high-pitched cry and an exaggerated Moro reflex.

Seizures have been reported with withdrawal from opioids, benzodiazepines, barbiturates, propofol, and inhalational anesthetic agents while visual and auditory hallucinations have been described with opioid, benzodiazepine, barbiturate, and inhalational anesthetic withdrawal. GI manifestations including emesis, diarrhea, and feeding intolerance may be especially prominent in neonates and infants. When such problems occur in the absence of other signs and symptoms of withdrawal, they may be attributed to other problems and not withdrawal. Activation of the sympathetic nervous system with tachycardia, hypertension, dilated pupils, and tachypnea is a prominent finding with withdrawal from any of the above-mentioned sedative/analgesic agents. Additional signs and symptoms of sympathetic hyperactivity include nasal stuffiness, sweating, and fever.

Treatment of withdrawal and clinical scoring systems

As with most problems that arise in clinical medicine, effective treatment starts with prevention. Given that the incidence of withdrawal is related to the total amount of medication administered, careful titration of the sedative or analgesic agents using clinical sedation scales is optimal. There are currently no data to support or refute the efficacy of so-called drug holidays during the use of sedative and analgesic agents in the PICU setting. This practice involves turning off sedative and analgesic agents until the patient responds and then restarting the infusions at half of the previously used infusion rate. This practice effectively provides the same rationale as using clinical sedation scores in that excessive infusion rates are avoided. However, many physicians and certainly bedside nurses are hesitant to discontinue effective sedation and analgesia at times when painful processes may be present in the critically ill patient. Additionally, concerns have been raised that this practice may result in periods of excessive agitation in critically ill patients. Before such practices are universally embraced, prospective trials in the pediatric population are needed to demonstrate not only their efficacy but also their safety.

Prospective studies are needed to better address the efficacy of rotating sedation regimens, intermittent vs. continuous infusions of sedative/analgesic agents, and the role of other pharmacologic agents such as NMDA receptor antagonists and magnesium in preventing tolerance and dependency. Until further investigations provide additional insight into the factors controlling opioid dependency and ways of preventing or delaying

it, PICU physicians will be faced with a group of patients who require specific actions to prevent the development of withdrawal symptoms. Treatment strategies and protocols are necessary so that the problems associated with tolerance, physical dependency, and withdrawal do not limit the administration of these agents in the PICU population.

In order to provide effective therapy for patients with withdrawal, it may be helpful to identify those patients who are most likely to manifest symptoms of withdrawal and also to have scoring systems to identify and quantitate the signs and symptoms of withdrawal. As noted previously in this chapter, risk factors that have been identified include not only the total dose of the sedative or analgesic agent that has been administered but also the duration of the infusion.

In a prospective trial of 23 infants and children who had received fentanyl infusions for sedation during mechanical ventilation, Katz et al. determined the factors that could be used to identify the group who was at risk of withdrawal [360]: The total fentanyl dose and the duration of the infusion correlated with the risk of withdrawal, whereas the maximum fentanyl infusion rate did not. A total fentanyl dose ≥1.5 mg/kg or an infusion duration ≥5 days was associated with a 50% incidence of withdrawal, whereas a total fentanyl dose ≥2.5 mg/kg or an infusion duration ≥9 days was associated with a 100% incidence of withdrawal. Fonsmark et al. reported an increased probability of withdrawal in patients who received a total dose of midazolam ≥60 mg/kg or a total dose of pentobarbital ≥25 mg/kg [352].

Scoring systems may be helpful in the management of patients presenting with signs and symptoms of withdrawal, not only in identifying the behaviors or withdrawal but also in grading its severity and judging the response to therapy. Unfortunately, the majority of scoring systems were developed to deal with neonates born to drug-addicted mothers and therefore may not be applicable to the PICU population [361].

To address such issues, Ista et al. reviewed the literature regarding withdrawal scoring systems and found that of the six available in the literature, only two were directed toward the PICU population [362]. The first of these included the Sedation Withdrawal Score (SWS), which assigns points (0–2) to 12 withdrawal behaviors, thereby providing a maximum score of 24. The signs and symptoms are grouped to the CNS (tremor, irritability, hypertonicity, high pitched cry, convulsions, and hyperactivity), the GI system (vomiting and diarrhea), and the autonomic nervous system (fever, sweating, sneezing, and respiratory rate) [363]. The decision regarding weaning of the current sedative and analgesic regimen is based on the score (0–6 wean, 6–12 no change, 12–18 revert to previous regimen, more than 18 reevaluate plan). Ista et al. expressed concerns that this scale has not been validated in children and that in particular, there are no data regarding its sensitivity, specificity, validity, and reliability.

The other scale is the Opioid and Benzodiazepine Withdrawal Scale (OBWS) [364]. The OBWS is a 21-item checklist that evaluates 16 specific withdrawal behaviors. Franck et al. evaluated their scale by performing 693 assessments in 15 children who varied in age from 6 weeks to 28 months. Using 8 as a cut-off score for the presence of withdrawal, the sensitivity of the OBWS was only 50% with a specificity of 87%. The predictive value in terms of positive and negative ratios was 4.0 and 0.57 (considered moderate for a diagnostic tool) while the interrater reliability was acceptable at 0.8.

Because of these issues, Ista et al. concluded that a more appropriate scale was necessary in the PICU population and went on to use the data from their review to develop their own withdrawal scale [365]. Their withdrawal scale included all of the behaviors that had been reported in the literature as manifestations of withdrawal in the pediatric-aged patient. From this, they developed the Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC), which included 24 withdrawal symptoms. Over a 6-month period, they collected 2,188 observations in 79 children within 24 h of tapering off and discontinuing sedative and/or analgesic medication. They noted that specific symptoms including agitation, anxiety, muscle tension, sleeping for less than 1 h, diarrhea, fever, sweating, and tachypnea were observed most frequently

and that longer duration of opioid or benzodiazepine use and high doses were risk factors for withdrawal. Twenty-three observations were scored simultaneously and resulted in an inter-observer correlation coefficient of 0.85 with a range of 0.59–1.0 for the individual items.

By maintaining a high index of suspicion and the use of withdrawal scores developed for the PICU patient, it seems that we are closer to our goal of identifying patients who are manifesting withdrawal symptoms. As mentioned previously, the mainstay of preventing withdrawal must be the identification of high-risk patients and the slow weaning of sedative and analgesic agents. Withdrawal scales should still be applied to these patients in the event that withdrawal occurs despite our attempts to prevent it. Based on limited evidence-based medicine, it has been suggested that, in patients who have received sedative and analgesic infusions for more than 5–7 days, weaning can be accomplished at a rate of 10–20% per day [366, 367]. However, these studies have reported a significant incidence of withdrawal using these protocols thereby suggesting that a more reasonable approach may be a 5–10% decrease per day as has been suggested for adult patients and supported by some in the PICU population [368, 369].

When prolonged administration of opioids or other sedative agents will be necessary, switching to the oral administration of long-acting agents such as methadone may allow for earlier hospital discharge. This is especially true in patients who have received weeks of therapy and are on large doses of opioids and/or benzodiazepines. Advantages of methadone include its longer half-life allowing for dosing 2–3 times per day, an oral bioavailability of 75–90%, and availability as a liquid. Although the first report regarding the use of methadone suggested a starting dose of 0.1 mg/kg every 12 h, the three patients in the series were receiving relatively low opioid doses and, therefore, higher doses of methadone were not needed [349]. Clinical experience of this author has indicated that higher doses of methadone may be needed, depending on the dose of fentanyl. When considering the appropriate dose transition from intravenous fentanyl to oral methadone, consideration should be given to the differences in the potency and half-life of the two medications as well as cross-over tolerance [370]. Similar considerations are necessary when switching from intravenous midazolam to oral lorazepam.

Lugo et al. in a study evaluating enteral lorazepam to decrease midazolam requirements during mechanical ventilation suggested starting at a lorazepam dose that was 1/6th that of the total daily dose of intravenous midazolam [82]. Once the appropriate enteral/oral dose is determined and started, the intravenous administration is tapered off quickly.

After the initial reports regarding the use of methadone, other authors have suggested variations in conversion ratios from fentanyl to methadone as well as dosing intervals and most importantly weaning schedules [366, 367, 371–373]. Some have used intravenous methadone prior to oral methadone during the initial conversion process. Regardless of the protocol used, close observation during the conversion period is necessary to avoid adverse effects from oversedation or to recognize the early symptoms of withdrawal.

There remain some stigmata concerning the use of methadone. Therefore, a thorough discussion with the parents is necessary to discuss why methadone is being used and to outline the differences between addiction and physical dependency. Because of these issues as well as familiarity with long-acting morphine preparations, which are used in the treatment of children with chronic cancer-related pain, some physicians prefer to use the latter agent. However, these agents are available only in tablets that cannot be crushed so that administration and subsequent weaning protocols may be more difficult in younger patients. Methadone on the other hand is available in a liquid formulation. More recently, concern has been expressed for the adult who is on maintenance methadone for drug addiction regarding the potential for death, the potential for QT prolongation and arrhythmias [374]. To date, there are no such reports from the pediatric population; however, these concerns have led to the consideration of obtaining periodic ECG's

prior to and after instituting therapy with methadone.

A final issue with methadone is its metabolism by the P_{450} isoenzyme system of the liver making alterations in metabolism possible based on genetic factors and the coadministration of other medications. These factors should be considered when methadone is started or other medications are added to the patient's regimen.

In addition to opioids, nonopioid agents have been used to treat opioid withdrawal. In the author's opinion, this is less than optimal because it seems to make physiologic sense when dealing with the problems of tolerance and dependence to replace the missing agent rather than to treat the resulting symptoms. The benzodiazepine, diazepam, has been used to treat opioid withdrawal in neonates and infants [375].

When benzodiazepines are used to treat opioid-withdrawal in neonates born to drug-addicted mothers, clinical studies have demonstrated adverse effects on behavior including increased sedation and poor sucking as well as poor control of the autonomic hyperactivity that occurs with opioid withdrawal [376]. Similar results have been demonstrated with the use of phenobarbital [377, 378].

Phenothiazines (chlorpromazine) have also been used in the treatment of infants of drug-addicted mothers [379]. Despite relative success with an efficacy equivalent to that of phenobarbital, adverse effects including α-adrenergic blockade with hypotension and a lowering of the seizure threshold have limited their widespread application [380].

The centrally acting, α_2-adrenergic agonist, clonidine, has been used to treat and prevent opioid withdrawal in both neonates and adults [381–383]. Alpha$_2$-adrenergic receptors mediate part of their pharmacologic actions through the activation of the same potassium channel as opioid receptors. Because of its prolonged duration of action (12–18 h), once or twice a day dosing is possible. Starting doses range from 3 to 5 μg/kg/day.

Adverse effects from clonidine include sedation, bradycardia, and hypotension. Although the use of clonidine is becoming more widespread in pediatric anesthesia as a premedicant in the operating room as well as for caudal/epidural anesthesia; to date, there is limited clinical experience with its use in the treatment of opioid withdrawal.

Dexmedetomidine (Precedex®, Hospira Worldwide Inc, Lake Forest, IL) is the pharmacologically active dextro-isomer of medetomidine. Like clonidine, it exerts its physiological effects via α_2-adrenergic receptors. Regardless of the agent or agents responsible for withdrawal, the role of dexmedetomidine in treating such problems is supported by animal studies [313–316], case reports in adults and children [317–321], and one retrospective case series in infants [322].

The largest series reported in either the adult or pediatric population regarding the use of dexmedetomidine to control withdrawal is a retrospective review of seven infants ranging in age from 3 to 24 months [322]. The patients had received a continuous fentanyl infusion supplemented with intermittent doses of midazolam during mechanical ventilation. Withdrawal was documented and successfully treated with a bolus and subsequent infusion of dexmedetomidine. More recently, the feasibility of subcutaneous administration to treat or prevent withdrawal in infant and children has been demonstrated [384].

Delirium

In addition to the myriad of issues surrounding the provision or sedation and analgesia to critically ill patients, recent attention in clinical practice and in the literature, especially in the adult ICU population, has been focused on the issue of delirium following critical illnesses. In the ICU setting, delirium has been described as an acute and fluctuating disturbance of consciousness and cognition. In more general terms, the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) has defined delirium as a disturbance of consciousness and cognition that develops over a short period of time and fluctuates over time.

Over the years, several different terms and labels have been used to describe this syndrome in the ICU setting including ICU psychosis, ICU

syndrome, acute confusional state, encephalopathy, and acute brain failure. However, with a greater appreciation of the importance of this syndrome on the outcomes of critically ill patients and the need to appropriately identify it, the critical care community has recently conformed to the recommendations of the APA that the term "delirium" be used uniformly to describe this syndrome of brain dysfunction.

Delirium may occur in up to 80% of critically ill adults. Its short and long-term consequences include prolonged hospitalization as well as other morbidities. It may also be either a marker for or a direct cause of both short-term and long-term mortality risk of ICU patients [385, 386].

In a prospective evaluation meant to determine the immediate and long-term consequences of delirium in a cohort of 224 adult ICU patients, 183 (81.7%) developed delirium at some point during their ICU stay [387]. Demographics including age, comorbidity scores, dementia scores, activity of daily living scores, severity of illness, and admitting diagnosis were similar between those patients who developed delirium and those who did not. Patients who developed delirium had a higher 6-month mortality rate (34 vs. 15%, $p=0.03$) and spent 10 days longer in the hospital than those patients who did not develop delirium ($p<0.001$). Additional morbidities related to delirium included prolonged ICU stay, prolonged duration of requirements for mechanical ventilation, and increased costs of care following hospital discharge [385–388].

Classification of delirium

Given difficulties with identification, even in the adult population, delirium may often go unrecognized or attributed to other diseases processes or comorbid conditions such as dementia and depression or considered a natural, acceptable complication of a critical illness. Delirium can generally be divided into hypoactive and hyperactive subtypes, which outside of the ICU population have been shown to have some prognostic values. Hypoactive delirium, which tends to account for the majority of cases in the ICU setting, is characterized by decreased responsiveness, withdrawal behaviors, apathy, and depression. Hyperactive delirium, as the name implies, is characterized by agitation, restlessness, and emotional lability [389].

In a prospective evaluation of delirium in a cohort of adult medical ICU patients, Peterson et al. reported that purely hyperactive delirium was uncommon, occurring in 1.6% of the patients, hypoactive delirium occurred in 43.5% of the patients while 54.1% had mixed delirium [390]. Ouimet et al. proposed an alternative scheme for the categorization of delirium in the ICU setting, which is based on the number of symptoms of delirium that are present [391]. Six hundred ICU patients were observed for symptoms of delirium and then categorized according to the number of symptoms present. No delirium was present if there were no symptoms, patients with four or more symptoms were classified as having "clinical delirium" while an intermediate state which the authors termed "subsyndromal delirium" was thought to be present in patients who manifested 1–3 symptoms.

Diagnosis of delirium

Given its impact on short and long-term outcome in the ICU patient, the accurate diagnosis of delirium is mandatory to identify its occurrence following critical illness and to facilitate trials to determine ways to limit its occurrence. As noted previously, the underdiagnosis and recognition of delirium remain a significant problem [392]. Such issues have led to the suggestion by the Society for Critical Care Medicine that some type of delirium screening tool should be used in all critically ill patients. As with depth of sedation and withdrawal, there are instruments which have been validated for the assessment of delirium in ICU patients. To date, these instruments have only been studied in the adult population. Two such tools are (1) the Intensive Care Delirium Screening Checklist (ICDSC) and the (2) Confusion Assessment Method for the ICU (CAM-ICU) [393, 394] (Table 13.4). The scoring systems allow the

Table 13.4 The intensive care delirium screening checklist

Patient evaluation	Day 1	Day 2	Day 3	Day 4	Day 5
Altered level of consciousness* (A–E)					
If A or B do not complete patient evaluation for the period					
Inattention					
Disorientation					
Hallucination—delusion—psychosis					
Psychomotor agitation or retardation					
Inappropriate speech or mood					
Sleep/wake cycle disturbance					
Symptom fluctuation					
Total score (0–8)					

* Level of consciousness:
A: No response, score: None
B: Response to intense and repeated stimulation (loud voice and pain), score: None
C: Response to mild or moderate stimulation, score: 1
D: Normal wakefulness, score: 0
E: Exaggerated response to normal stimulation, score: 1
(reproduced from Bergeron et al. [393], with permission from Springer)

assessment and diagnosis of delirium in ICU patients by nonpsychiatric-trained physicians and healthcare workers in the ICU. These tools can be used even in patients who are unable to speak because of the presence of an ETT.

Both scoring tools begin with an assessment of the patient's responsiveness and no further evaluation is undertaken if the patient is obtunded or deeply sedated. The ICDSC rates the level of consciousness from A to E, with A denoting no response and E denoting exaggerated response to normal stimulation. If an A (no response) or B (response to intense or repeated stimulation) is obtained, no further assessment is undertaken. For patients who manifest a C, D, or E level, a further evaluation for the presence of delirium is undertaken. This includes assessing inattentiveness, disorientation, hallucination-delusional-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep–wake cycle disturbances, and symptom fluctuation. These seven checklist items are added to altered level of consciousness to give eight possible items which are scored as present or absent to give a total delirium score of 0–8 with four or more considered diagnostic of delirium.

Risk factors for the development of delirium

As with many outcomes in the ICU, the risk factors for the development of delirium include factors that may be present prior to the onset of the acute illness and those that relate directly to the acute illness or medications administered during it. Patient comorbidities that may increase the likelihood of delirium include advanced age, hypertension, the severity of illness, history of tobacco use, and baseline cognitive impairment. Other potential risk factors include metabolic disturbances (plasma levels of sodium, calcium, and blood urea nitrogen), acute infection, respiratory disease, acidosis, anemia, and hypotension. Additionally, there may be some genetic predisposition to the development of delirium.

Ely et al. evaluated the possible association of the apolipoprotein E genotype and delirium among 53 mechanically ventilated medical ICU patients [395]. Patients with the apolipoprotein-4 polymorphism (a risk factor for Alzheimer's disease) manifested delirium twice as long as those without this polymorphism. The duration of delirium (median and interquartile range) was 4 days (3–4.5 days) vs. 2 days (1–4 days, $p = 0.05$).

Also of significant concern in the ICU patient is the potential association between delirium and medications used for sedation or analgesia. To date, the most compelling evidence suggests that medications which act through the GABA system increase the likelihood of delirium. Most notable of the GABA-agonists in the role of delirium are the benzodiazepines including both midazolam and lorazepam [396].

There are little or no data to demonstrate any relationship between the use of opioids such as morphine or fentanyl and the risk of developing delirium. Rather, the appropriate use of opioids for analgesia may decrease its incidence: Ouimet et al. reported that the mean daily dose of opioid dose was higher among patients without delirium than among those with delirium [397]. Similarly, in a cohort of 541 adult patients who were hospitalized for a hip fracture, those who received more than 10 mg/day of parenteral morphine or morphine-equivalents were less likely to develop delirium than patients who received less analgesia [398]. Treatment with meperidine was an exception as meperidine has been shown to increase the risk of delirium when compared with other opioids.

Pathophysiology of delirium

The exact cellular or physiologic mechanisms of delirium remain poorly defined. Additionally, it is likely that it may result from a multifactorial process, resulting from a combination of underlying patient factors, the critical illness, and medications used in the ICU setting. One theory that has been supported by clinical research is that delirium results from a neurotransmitter imbalance. Derangements of several different central neurotransmitters have been theorized to result in delirium, although the greatest focus has been on alterations in the central concentrations of dopamine and acetylcholine [399, 400]. Specifically, an excess of dopamine or relative deficiencies in acetylcholine may result in delirium. Other potential central neurotransmitters which may play a role in the pathogenesis of delirium include GABA, serotonin, endorphins, and glutamate [401, 402]. Other evidence has pointed toward inflammation as a potential etiologic factor in the development of delirium. Animal studies have demonstrated that an inflammatory cascade may result in alterations in the blood–brain barrier, changes in vascular permeability within the CNS, and EEG changes consistent with those seen in ICU patients who develop delirium [403]. The end result of this inflammatory process may provoke delirium through alterations in CBF, by interfering with normal neurotransmitter function, or altering neurotransmitter concentrations within the CNS.

Prevention and treatment of delirium

Given the prevalence and adverse effects of delirium in the ICU setting, appropriate interventions include not only treatment once delirium has occurred but also potentially strategies to limit its incidence. Although performed in a non-ICU population, Inouye et al. nonrandomly assigned 852 hospitalized elderly patients to usual care or management with a multiple component strategy aimed at decreasing the incidence of delirium [404]. The interventions included repeated reorientation of the patient, the provision of cognitively stimulating activities, a nonpharmacologic protocol to improve sleep, ambulation and mobilization activities, range of motion exercises, timely removal of catheters and physical restraints, and improvement in sensory input through the use of eyeglasses, magnifying lenses, and hearing aids. These interventions significantly reduced the incidence of delirium (15.0% in the standard care group vs. 9.9% in the intervention group). Given the outcome of this and other similar trials, such protocols have been recommended for use in the ICU. It must also be recognized that the use of sedative medications increases the incidence of delirium and efforts should be made to minimize dosages [405].

Haloperidol has been recommended as the drug of choice for the treatment of ICU delirium by both the Society of Critical Care Medicine and the APA. Classified as a typical antipsychotic, haloperidol blocks dopamine$_2$ receptors thereby

decreasing agitation, hallucinations, and delusions. Given the lack of prospective, clinical trials, the optimal dose regimen has not been defined. Recommendations from the Society of Critical Care Medicine for adults include an initial dose of 2 mg intravenously, followed by repeated doses (doubling the previous dose) every 15–20 min until the agitation is controlled. Once the agitation subsides, scheduled doses (every 4–6 h) are recommended for 2–3 days followed by a tapering of the dose once the problem has resolved. In addition to its use as treatment for acute delirium, haloperidol has been shown to be effective when used as a prophylactic agent to prevent delirium in a cohort of elderly patients [406]. The atypical antipsychotics (risperidone, ziprasidone, quetiapine, and olanzapine) may also be helpful in the treatment of delirium, but only preliminary data exist supporting their use in the ICU [407].

Patients treated with haloperidol or other antipsychotics should be monitored for adverse effects including cardiac arrhythmias due to effects on repolarization (these effects are less common with the atypical antipsychotic agents), hypotension, dystonic reactions, extrapyramidal effects, malignant neuroleptic syndrome, and lowering of the seizure threshold. Given the potential for the development of lethal cardiac arrhythmias including torsades de pointes, these agents are contraindicated in patients with a prolonged QT interval. Anticholinergic effects such as dry mouth, constipation, and urinary retention may also occur.

Summary

A cookbook approach to sedation and analgesia in the PICU is not feasible due to the wide variation in patients, ages, comorbid diseases, and clinical scenarios faced in this population. As no single agent will be effective in all patients and all scenarios, healthcare providers must be facile with the use of a wide array of sedative and analgesic agents. The three primary choices that must be made when choosing a sedative/analgesic agent are the agent, its route or delivery, and the mode of delivery.

In most scenarios, sedation during mechanical ventilation is initiated with either a benzodiazepine or an opioid. There is an abundance of clinical experience with midazolam in the PICU population although lorazepam may provide an effective alternative with a longer half-life and more predictable pharmacokinetics without the concern of active metabolites. However, there are limited reports regarding its use in the PICU population and there may be concerns regarding accumulation of the diluent, propylene glycol.

Although fentanyl is frequently chosen because of its hemodynamic stability and beneficial effects on PVR, morphine is an effective alternative with data to suggest that the development of tolerance may be slower and that there may be fewer issues with withdrawal when compared to fentanyl. Long-term follow-up studies have demonstrated no adverse CNS developmental effects from morphine use in neonates and infants. In the critically ill infant at risk for pulmonary hypertension, the literature continues to support the use of the synthetic opioids given their ability to modulate PVR and prevent pulmonary hypertensive crisis. When these agents fail or lead to adverse effects, alternatives include ketamine, pentobarbital, or dexmedetomidine.

Ketamine may be useful for the patient with hemodynamic instability or with increased airway reactivity as a component of their disease process. To date, there are limited reports regarding the use of pentobarbital in the PICU with recent concerns being raised regarding a high incidence of adverse effects associated with its use. Propofol has gained great favor in the adult population as a means of providing deep sedation while allowing for rapid awakening. Similar beneficial properties are achieved in the pediatric-aged patient; however, concerns of the propofol infusion syndrome have significantly limited its use in the PICU population. As the pediatric experience increases, it appears that there will be a role for newer agents such as dexmedetomidine. The use of dexmedetomidine may continue to increase as the incidence of delirium has been shown to be less with its use when compared to commonly used benzodiazepines [408]. Suggested starting guidelines for sedative and analgesic agents are outlined in Table 13.3.

The second decision regarding PICU sedation includes the mode of administration. Effective sedation and analgesia are generally most easily achieved with the use a continuous infusion of a benzodiazepine or opioid supplemented with as needed bolus doses to provide additional analgesia or sedation. These bolus doses are given during periods of breakthrough agitation or prior to noxious stimulation such as tracheal suctioning or other nursing interventions. Patients requiring frequent bolus doses should have the baseline infusion rate increased. As the infusion rate is increased, the bolus doses should be increased to equal the hourly rate. The titration of the infusion and use of supplemental bolus doses should be adjusted using clinical sedation scales.

The third decision regarding sedative and analgesic agents is the route of administration. In the PICU setting, the intravenous route is used in the vast majority of patients. However, specific circumstances may exist which necessitate the use of a nonintravenous route. Although medications such as midazolam have been administered via many nonparenteral routes including oral and transmucosal administration, these routes will have a limited role in the PICU population although they are viable options for procedural sedation. The subcutaneous route may be used in specific circumstances while future clinical trials with inhalational anesthetic agents may provide us with more information regarding these agents in infants and children.

When sedative and analgesic agents are administered, adverse effects on physiologic function may follow [341]. Monitoring of the patient's physiologic function is mandatory whenever these agents are in use. There is also an increased understanding and recognition of withdrawal syndromes which may occur following the prolonged administration of sedative and analgesic agents. Strategies are needed to identify those patients at risk for withdrawal followed by appropriate interventions to prevent or treat it. With these caveats in mind, the goal of providing effective and safe sedation and analgesia for all of our patients is within reach.

Case Studies

Case 1

A 10-year-old, 48 kg boy is brought to the emergency room following a motor vehicle accident. His injuries included a closed head injury and a right femur fracture. A computed tomography scan is requested to rule out intra-abdominal injuries. His vital signs are stable and his Glasgow Coma Scale is 11. His neck is stabilized in a hard cervical collat. He is sleepy, but has intermittent periods of combative behavior. Sedation is requested for the CT imaging.

***Considerations*:** This patient's altered mental status and potential for a full-stomach make sedation without control of the airway potentially problematic in that loss of airway reflexes may result in upper airway obstruction, the need for bag-valve-mask ventilation with the risks of aspiration. Given these concerns, the decision is made not to provide with sedation, but rather to protect the airway with endotracheal intubation and induce general anesthesia. Given the potential for associated injuries which may result in blood loss and decreased intravascular volume, etomidate is chosen for the induction of general anesthesia.

***Drugs*:** Etomidate (Amidate, Abbott Pharmaceuticals) is an intravenous anesthetic agent, introduced into clinical practice in 1972, whose primary effects of sedation and amnesia are mediated through the GABA inhibitory neurotransmitter system. Following intravenous administration, loss of consciousness is rapid (15–20 s) and as with propofol and the barbiturates, its duration of action following a single bolus dose is related

to redistribution rather than metabolism and clearance. Beneficial CNS effects include a decrease of the $CMRO_2$, CBF, and ICP. CPP is maintained because of minimal effects on myocardial function. Although the barbiturates and propofol have similar effects on CHS dynamics, the latter agents are likely to decrease MAP and thereby decrease CPP. Myoclonic movements are also a frequently observed effect following the rapid intravenous administration of etomidate. Although these movements may simulate tonic-clonic seizure activity, no epileptiform discharges are noted. It has been suggested that the myoclonic movements are of spinal origin resulting from disinhibition of inhibitory neuronal pathways. Pretreatment with fentanyl, benzodiazepines, or a small dose of etomidate has been shown to be effective in decreasing the incidence of myoclonus. The most significant concern with etomidate and the factor that limits its long-term administration in the ICU setting is its effects on the endogenous production of corticosteroids. This effect was identified when an increased risk of mortality was noted in adult ICU patients who were sedated with a continuous infusion of etomidate. Etomidate inhibits the enzyme, 11-b hydroxylase, which is necessary for the production of cortisol, aldosterone, and corticosterone. To date, significant controversy surrounds the clinical significance of the adrenal suppression following a single induction dose of etomidate with some authors calling for the abandonment or at least a reevaluation of the use of etomidate. The duration of the adrenal suppression produced by a single induction dose of etomidate has varied from study to study, but may exceed 12 h. However, no study has demonstrated changes in clinical outcome based on the adrenal suppression following a single dose of etomidate. Therefore, no definite decision can be reached regarding whether the use of etomidate should be eliminated from clinical practice and even in the scenario presented, its use may be considered somewhat controversial. Given its effects on cerebral dynamics, it also should be considered for patients with increased ICP with or without associated myocardial dysfunction. A rapid sequence intubation is performed with manual in-line stabilization following the administration of etomidate and succinylcholine. This is followed by a propofol infusion starting at 25 mg/kg/min and titrated up based on the hemodynamic response to allow for completion of the CT scan. Following this, the patient is admitted to the Pediatric ICU and his trachea is extubated once his mental status has returned to baseline.

Case 2

A 26-month-old infant is recovering from surgery for congenital heart disease. Following the surgical procedure, the infant is sedated with a fentanyl infusion with intermittent doses of midazolam for 4 days during mechanical ventilation. In anticipation of extubation, the fentanyl which was infusing at 8 μg/kg/min and the intermittent doses of midazolam are discontinued. Three hours later, the infant is tachycardic, hypertensive, has dilated pupils, and a temperature of 38.6°C.

***Considerations*:** This infant is likely manifesting signs and symptoms of withdrawal; however, other possibilities must be excluded as the diagnosis of withdrawal is a diagnosis of exclusion. The work-up would include a thorough physical examination and perhaps laboratory evaluation including a complete blood count and blood gas analysis to rule out hypercarbia, hypoxemia, decreased cardiac output, and infection. Although this patient falls below the 50% incidence of withdrawal given that the infusion was continued for only 4 days, withdrawal may still occur in this patient. Some type of withdrawal scale that is specific for the Pediatric ICU patient may help to identify the severity of the withdrawal as well as the

response to therapy. The OBWS is a 21-item checklist that evaluates 16 specific withdrawal behaviors. The patient scores a 12 indicative of withdrawal. Given the brief duration of the fentanyl infusion, it is decided that weaning may be accomplished relatively rapidly without affecting the duration of the PICU stay. Therefore, the decision is made to reinstitute intravenous therapy.

***Drugs*:** Given that this patient is extubated and breathing spontaneously, it is decided to use dexmedetomidine which may have less effect on ventilatory function than opioids or benzodiazepines. Dexmedetomidine is the pharmacologically active dextro-isomer of medetomidine. Like clonidine, it exerts its physiological effects via α2-adrenergic receptors. Dexmedetomidine and clonidine are members of the imidazole subclass which exhibits a high ratio of specificity for the α2 vs. the α1 receptor. However, while clonidine exhibits an α2:α1 specificity ratio of 200:1, that of dexmedetomidine is 1,600:1 thereby making it a complete agonist at the α2-adrenergic receptor. Dexmedetomidine has a short half-life (2–3 vs. 12–24 h for clonidine) and is commercially available for intravenous administration. Adverse effects are generally limited with dexmedetomidine although hemodynamic effects (bradycardia or hypotension) may occasionally be seen. As with clonidine, there is increasing experience and interest regarding the use of dexmedetomidine in the prevention and treatment of withdrawal following the prolonged administration of opioids and benzodiazepines in the PICU setting. Regardless of the agent or agents responsible for withdrawal, the role of dexmedetomidine in treating such problems is supported by animal studies, case reports in adults and children, and one retrospective case series in infants. A loading dose of dexmedetomidine (0.5 μg/kg) was administered over 10 min followed by an infusion of 0.5 μg/kg/h. Ongoing OBWS values decreased to 1–3 over the ensuring 3–4 h. The dexmedetomidine was decreased in increments of 0.1 μg/kg/h with constant observation of the OBWS. Alternatively, dexmedetomidine can also be administered subcutaneously if there is a need to remove central lines and eliminate the need for vascular access.

Case 3

A 10-month-old infant is admitted to the PICU following direct laryngoscopy and airway laser in the operating room. Direct laryngoscopy revealed a subglottic hemangioma which was effectively treated with the laser and the patient remains intubated with a 4.0 ETT given concerns of edema and airway swelling. The otolaryngologist requests overnight sedation (16–18 h) to ensure that the airway edema has resolved and that the trachea can be successfully extubated. On arrival in the PICU, the infant is initially comfortable with a Ramsay sedation score of 4. Sedation is initiated with morphine at 30 μg/kg/h and midazolam at 0.5 mg/kg/h. The patient gradually becomes more awake and then agitated with Ramsay scores of 1. Four bolus doses of midazolam (0.1 mg/kg) and two of morphine (0.05 mg/kg) are given and the morphine infusion is increased to 50 and then to 100 μg/kg/hr while the midazolam infusion is increased to 0.25 mg/kg/h. Four hours later, the patient's Ramsay scores are 1–2 again.

***Considerations*:** The goals of sedation in this patient are to maintain a deep level of sedation and then rapid awakening to ensure full respiratory function and upper airway control prior to endotracheal intubation. In a small subset of patients, the usual combination of an opioid (morphine or fentanyl) and midazolam fails to provide the needed depth of sedation. An additional concern with this combination is that these agents demonstrated a context-sensitive half-life whereby prolonged awakening may occur following a brief-duration infusion of more than 12–24 h.

***Drugs*:** There are a couple of options for this patient including the use of potent inhalational anesthetic agents, propofol or remifentanil. To date, there remain limited data regarding the use of the potent inhalational anesthetic agents for sedation in the PICU setting. A benefit of these agents is the ability to rapidly control the depth of anesthesia as well as rapid awakening upon their discontinuation. These agents may have some effect on hemodynamic function, but are generally well tolerated in patients without comorbid cardiac diseases of hypovolemia. The major obstacles to the use of the inhalational anesthetics in the PICU patient are issues with administration, monitoring, scavenging, and environmental pollution. Although techniques are available to allow the administration of these agents through ICU ventilators, the added cost and logistic issues limit their use. Given the problems with the devices and techniques currently available for the delivery of the potent inhalational anesthetic agents in the ICU setting, novel means of delivering these agents are needed. The Anesthetic Conserving Device or "AnaConDa®" is a modified heat-moisture exchanger with a deadspace of 100 mL which may allow a simplified means of administering the potent inhalational anesthetic agents in the ICU setting. The device is placed between the Y-piece of the ventilator circuit and the 15 mm adaptor of the ETT. There is also a port at the end of the device just proximal to its attachment to the ETT which allows gas sampling and monitoring of the agent concentration. The desired inspired concentration is titrated by adjusting the infusion rate on the syringe pump based on the manufacturer's recommendations. Exhaled isoflurane is adsorbed to the lipophilic carbon particle filter in the device and redelivered to the patient thereby limiting environmental pollution.

Another option would be the short-term infusion of propofol. Propofol is an alkyl phenol compound (2,6-diisopropylphenol) with general anesthetic properties. Although its chemical structure is distinct from that of other intravenous anesthetic, its mechanism of action is similar as it acts through the GABA system [170]. Although propofol was initially introduced into anesthesia practice for the induction and maintenance of anesthesia, its rapid onset and recovery times led to its eventual use for sedation in the ICU setting. When compared with midazolam for sedation in adult patients, propofol has been shown to provide shorter recovery times, improved titration efficiency, reduced post-hypnotic obtundation, and faster weaning from mechanical ventilation with limitation of issues surrounding context-sensitive half-life. Despite its potential benefits in the ICU setting and its efficacy for providing sedation during mechanical ventilation, the routine use of propofol is not recommended and, in fact, is considered contraindicated by many authorities because of the potential for the development of what has been termed the "propofol infusion syndrome." First described in 1992, the disorder includes metabolic acidosis, bradycardia, dysrhythmias, rhabdomyolysis, and fatal cardiac failure. Given these concerns, the manufacturer of propofol has cautioned against its use in the PICU patient. In specific clinical scenarios, propofol is still used as a short term drug (6–12 h) to transition from other agents such as fentanyl and midazolam to allow for more rapid awakening when we are ready for tracheal extubation. In these cases, intermittent monitoring of acid–base status is suggested with discontinuation of the propofol infusion should acidosis develop.

The final option is remifentanil. Remifentanil is a synthetic opioid that is metabolized by nonspecific esterases in the plasma. It has a clinical half-life of 5–10 min and a brief duration of effect even following 12–24 h of continuous infusion. These pharmacokinetic parameters hold true even in the neonatal population, making remifentanil the only opioid whose pharmacokinetics is not altered by gestational or chronologic age. Given these

properties, it is a potentially useful agent for providing a deep level of sedation and yet allowing for rapid awakening with discontinuation of the infusion even in the neonatal population. Although there is significant clinical experience with the use of remifentanil during surgical procedures in patients of all ages; to date, there are only anecdotal reports regarding its use in the PICU population. However, these reports demonstrate rapid control of the depth of anesthesia and rapid awakening when the infusion is discontinued. Unlike other opioids, remifentanil does not demonstrate a context-sensitive half-life and its duration of action remains constant even with a prolonged issue. Issues include the rapid development of tolerance, limiting its efficacy for more than 24 h as well as cost.

Remifentanil is chosen to provide sedation. An infusion is started at 0.2 μg/kg/min and the morphine infusion is discontinued after 15 min. The remifentanil is increased to 0.3 μg/kg/min and the midazolam infusion is incrementally decreased and discontinued after 2 h. Over the next 12 h, the Ramsay scores are 4–5 and the infusion is increased to 0.4 μg/kg/min. The next morning, an airleak is present around the ETT and upper airway examination in the PICU reveals no concerns of airway edema. The remifentanil infusion is discontinued and 15 min later, the patient's trachea is extubated without difficulty.

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Sedation for Pediatric Gastrointestinal Procedures

14

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Introduction

There is no single sedative or combined sedation regimen that has been identified as ideal for pediatric gastrointestinal (GI) procedures. General anesthesia and intravenous (IV) sedation remain the two primary options. General anesthesia requires the presence and expertise of an anesthesiologist or Certified Registered Nurse Anesthetist, and may involve inhalational or intravenous anesthetics. IV sedation is aimed at maintaining the child's ability to breathe spontaneously with intact protective airway reflexes. Depending on the targeted and achieved depth of sedation, it may be administered by a physician or nurse, in the absence of an anesthesiologist.

Generally speaking, sedation or anesthesia is necessary for children to remain comfortable and cooperative during gastrointestinal procedures. Complications during pediatric endoscopy are more commonly attributed to the sedation than to technical mishaps from bleeding or perforation [1–4]. Improving efficacy and safety for the pediatric sedation of gastrointestinal procedures has been a topic of great interest among pediatric gastroenterologists (GI) for the past 3 decades [1, 5].

A 2005 survey of members of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) suggests that there is a wide practice variation in types of sedation employed for pediatric gastrointestinal procedures [5]. One third of all respondents reported performing the great majority of their cases with endoscopist-administered IV sedation, another third reported the majority with general anesthesia in hospital operating rooms, and the final third reported performing more than three quarters of their procedures with anesthesiologist-administered propofol in a dedicated endoscopy facility, outside of main operating rooms. Only 10% of respondents reported using general inhalational anesthesia for all procedures performed. Although the great majority reported using the hospital operating room, one quarter of respondents stated that it was almost always inconvenient to schedule [5].

This chapter reviews the range of sedation approaches and techniques for pediatric gastrointestinal endoscopy, with a focus on method of delivery in addition to benefits, limitations, and pitfalls of various regimens. The "traditional" and innovative options will be discussed, concluding with the controversial technique of Non-anesthesiologist Administered Propofol Sedation (NAAPS), an approach now applied for adult gastrointestinal procedures.

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Goals and Optimal Levels of Sedation for Pediatric GI Procedures

The primary purpose of sedation for children undergoing upper and lower endoscopies is to perform procedures safely, with minimal emotional and physical discomfort. Secondary goals may include amnesia, efficiency, and cost-effectiveness.

Optimal levels of sedation may vary depending upon the procedure. For upper endoscopy, one major goal is to avoid gagging and to increase patient cooperation. For colonoscopy, the goal is often to avoid visceral pain as the endoscope loops through the colon. For upper endoscopy, a combination of topical local anesthetic with orally administered anxiolysis prior to intravenous line insertion has been shown to improve pediatric patient tolerance and satisfaction [6, 7].

The goal of achieving moderate to light sedation must be balanced against the potential to become deeply sedated [8]. In some clinical situations, relative immobility may be the primary objective, rather than achieving a particular level of sedation [9]. Neither societal nor regulatory guidelines to date recognize that the depth of sedation does not predict immobility in children [10]. Gastroenterologists have measured sedation outcome using a number of different benchmarks (Table 14.1). To objectively compare regimens, it is preferable to adopt independent observers and standardized scales.

Table 14.1 Parameters of a successful sedation program

Ability to match sedation levels to individual patients in clinical circumstances
Adequacy of sedation so procedures are not rushed or pressured
Adequacy of amnesia
Speed of recovery of cognition
Speed of recovery of locomotion
Creating a relaxed, humane work environment for the sedation team
Cost-effectiveness
Timeliness and efficiency
Furthering the public's perception of the benevolence of the medical profession
Low incidence of sedation complications
Low incidence of incomplete procedures
Collegial willingness to learn and grow as experience accrues

Preprocedure Preparation and Patient Assessment

Sedation for pediatric gastrointestinal procedures should be tailored to a patient's physical status, in accordance with guidelines from the American Society of Anesthesiologists (ASA) [11–13]. Consideration of the patient's age, medical condition (ASA level), and developmental status when tailoring a sedation regimen is important. Recent data suggests that the smallest and youngest pediatric patients with the highest ASA classifications are at greatest risk for complications during gastrointestinal procedures [3].

When working with children undergoing gastrointestinal procedures, it has been noted that personality and psychosocial development stages may vary widely and impact a child's response to sedatives, the rapidity of effect and the depth achieved [14, 15]. Patients can be roughly divided into four different age groups: less than 6 months, greater than 6 months, school aged (4–11 years), and adolescents. Infants under 6 months of age may have little anxiety and tend to be sedated easily. Infants greater than 6 months who have developed "stranger anxiety" may more smoothly be sedated if parents remain next to them during induction. School-aged children manifest "concrete thinking" and may be surprisingly difficult to sedate, concealing their high anxiety levels [16]. Adolescents also may appear composed during preprocedure preparations, and then become disinhibited and anxious after initial doses of sedatives.

Especially in school-aged children, a relaxed, detailed, and reassuring discussion of what to expect during the procedure, including the insertion of an intravenous catheter, may decrease patient anxiety levels [15]. The use of topical anesthetics for IV insertion such as topical lidocaine cream, or oral anxiolytics, such as midazolam, may be warranted [7, 17]. Children who exhibit greater distress during the IV insertion have been shown to experience significantly greater distress and pain throughout the rest of the procedure [17].

Regardless of sedation regimens employed, it is essential to perform airway assessments at every step of the endoscopic process, beginning with the preprocedure evaluation and concluding in the recovery room. The decision to care for a child requires that the medical condition, ASA status, physical exam (airway in particular), and planned procedure is balanced against the location of the facility (free-standing vs. hospital based) and available resources.

All providers who care for children with gastrointestinal disorders should be schooled in airway assessment, including those who do the periprocedure assessment, the sedation provider, and the gastroenterologist. There is increasing interest among gastroenterologists to adopt a comprehensive grading system which incorporates the Mallampati score and a focused physical exam in order to determine a numerical score which represents airway risk and guides the planning (Table 14.2). In many endoscopy units, an Airway Assessment score of 4 prompts a mandated anesthesiology assessment.

Table 14.2 Airway assessment

	Score
Mallampati	
Class I – Uvula is completely visible	0
Class II – Partially visible uvula	0
Class III – Soft palate visible but not uvula	1
Class IV – Hard palate visible only, not soft or uvula	2
Mouth opening	
Greater than 3 cm	0
Less than 3 cm	2
Hyoid mental distance	
Greater than 3 cm	0
Less than 3 cm	1
Neck flexion/extension	
Normal	0
Limited	1
Rigid	4
	Score _____
Score of 4 or greater = anesthesiology consultation suggested	

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Beyond airway assessment, a careful review of the patient's gastrointestinal disorder, past history, as well as their prior experiences with sedation and procedures guides the triage of a child undergoing a gastrointestinal procedure. Some gastrointestinal disorders increase the riskiness of the procedure. In particular, upper gastrointestinal bleeds, anatomic or physiologic obstruction of the upper gastrointestinal tract, recent ingestion of blood or food, and septic patients who need common bile duct clearance will place a patient at higher risk for complications both from the procedures and from the sedation [18].

In addition, premature infants as well as older children with body mass indices (BMI) for age greater than the 85th percentile may also be at increased risk [19, 20].

Common IV Sedation Regimens for Pediatric Gastrointestinal Procedures

There are a variety of IV sedation options that have been described for children undergoing these procedures [21]. Table 14.3 lists commonly used sedatives for sedation for pediatric gastrointestinal procedures and their recommended dosages. In general, the most common IV sedation regimens used for pediatric endoscopy combine a narcotic analgesic (e.g., meperidine or fentanyl) with a benzodiazepine (e.g., diazepam or midazolam). A brief review of the important pharmacokinetic, pharmacodynamic, and clinical properties of those medications most commonly used for GI sedation, directed to the GI concerns, will follow. Chapter 8 provides a more thorough and detailed review of all sedative agents and adjuncts.

Fentanyl

As a fat-soluble narcotic that rapidly penetrates the blood brain barrier, fentanyl is considerably more potent and fast acting than both morphine and meperidine. Its onset of action is about 30 s after IV administration, and its opioid effects last

Table 14.3 Recommendations for dosages of drugs commonly used for IV sedation for pediatric gastrointestinal procedures[a]

Drug	Route	Maximum dose (mg/kg)	Time to onset (min)	Duration of action (min)
Benzodiazepines				
Diazepam	IV	0.1–0.3	1–3	15–30
	Rectal	0.2–0.3	2–10	15–30
Midazolam	Oral	0.5–0.75	15–30	60–90
	IV	0.05–0.15	2–3	45–60
	Rectal	0.5–0.75	10–30	60–90
Opioids				
Meperidine	IV	1–3	<5	120–240
	IM	1–3	10–15	120–180
Fentanyl	IV	0.001–0.005 (1–5 μg/kg in 0.5–1.0 μg/kg increments)	2–3	30–60
Ketamine	IV	1–3	1	15–60
	IM	2–10	3–5	15–150

[a]This table reflects common dosings and sedation considerations but must be interpreted and applied with caution. The table reflects the views of the author

about 30–45 min. IV Fentanyl should always be administered slowly, as it has been associated with the dangerous side effects of chest wall and glottic rigidity after rapid administration [22].

Fentanyl is variably metabolized by the liver, especially in young children. Delayed fentanyl excretion has been reported in neonates with compromised hepatic blood flow [23]. Several studies have suggested that fentanyl may not represent an ideal sedative for infants. In particular, it has been associated with significant apnea in infants less than 3 months of age [24]. The unique pharmacokinetics of fentanyl is certainly relevant to pediatric endoscopists. In particular, fentanyl's termination of action occurs with redistribution of drug metabolites from the plasma, rather than from metabolism, causing its potential respiratory depressive effects to outlast its opioid effects. Fentanyl should be administered to children slowly and in small increments, allowing for a minimum of several minutes between doses.

Midazolam

Midazolam is a benzodiazepine that is 3–6 times more potent than diazepam. It may be administered by many routes: IV, oral, rectal, intramuscular, and intranasal. When administered IV, the onset of action is 1–5 min, with peak effect achieved at 30 min to 1 h. Several pharmacokinetic studies have suggested that midazolam may be metabolized and excreted more rapidly in children than adults [7, 25, 26]. Midazolam is relatively unique among benzodiazepines in that its clearance appears to be dose related, with increased clearance at escalating dosage [27]. Pediatric gastroenterologists have reported the need to require larger weight-adjusted doses for pediatric vs. adult patients in order to achieve similar doses and duration of sedation [28].

Reversal Agents for Narcotics and Benzodiazepines

Reversal agents are available only for benzodiazepines and narcotics. Table 14.4 lists reversal agents and their recommended dosages for children. Although reversal agents have been used in adults to expedite recovery, it is important to recognize that there may be resedation as the effect of sedative outlasts that of the reversal agent [29, 30]. Most endoscopy and pediatric sedation guidelines stipulate that patients who receive a dose of a reversal agent should be monitored for an extended period, and administered repeat doses if necessary [31].

Table 14.4 Reversal agents for benzodiazepines and opioids and recommended dosages[a]

Drug	Class	Route	Dose (mg/kg)	Time to onset (min) action(min)	Duration of antagonist
Flumazenil	Benzodiazepines	IV (max 3 mg/h)	0.01	1–2	<60
Naloxone	Narcotics	IV/IM	0.1	2–5	20–60

[a]This table reflects common dosings and sedation considerations but must be interpreted and applied with caution. The table reflects the views of the author

Ketamine

Ketamine is a dissociative agent that largely spares upper airway muscular tone and laryngeal reflexes, and may represent an alternative to narcotics and benzodiazepines for sedating children for gastrointestinal procedures [32–40]. As a derivative of phencyclidine, ketamine binds to opiate receptors, and rapidly induces a trancelike cataleptic condition with significant analgesia. Routes of administration include oral or rectal, with intravenous or intramuscular more common for endoscopy.

Unlike most sedatives, ketamine is almost always effective at significantly immobilizing patients with minimal cardiac and respiratory effects, and is considered to have a broad margin of safety. It should be used with caution in patients less than 3 months of age, as well as those with histories of airway instability, tracheal abnormalities, active pulmonary disease, cardiovascular disease, head injury, central nervous system masses, hydrocephalus, porphyria, and thyroid disease [36, 37, 41]. Ketamine is considered by many to be contraindicated in patients with a history of psychosis [36, 37].

To date, the main drawback noted about ketamine sedation for pediatric procedures has been its association with hallucinogenic emergence reactions in some children [42–44]. Although it has been suggested that these effects can be lessened by the prior administration of a short-acting benzodiazepine, such as midazolam, recent evidence reveals that the midazolam does not decrease the agitation but rather may increase it in postpubertal children [44, 45]. Ketamine has also been associated with increased airway secretions and increased incidence of postoperative nausea and vomiting. During upper endoscopy, ketamine has been associated with a potential for laryngospasm [46, 47]. Although in the past, the prophylactic administration of anticholinergics was believed to reduce the incidence of secretions, laryngospasm, and respiratory complication, this is no longer held true. Rather, a recent matched case–control analysis of 8,282 ketamine procedures in the emergency department revealed no association between age, dose, procedure, medical status, route of delivery, and the administration of anticholinergics with the occurrence of laryngospasm [48]. This data is important because it identifies the occurrence of laryngospasm as an unpredictable and idiosyncratic reaction. All practitioners, thus, who administer ketamine should be prepared to identify and treat laryngospasm. Gilger et al. performed a retrospective review of 402 endoscopies (upper and lower) performed in children receiving different sedation combinations at Texas Children's Hospital. There were three groups: Group 1- midazolam + meperidine, Group 2- midazolam, meperidine + ketamine, Group 3- midazolam + ketamine. The midazolam + ketamine group had the lowest rate of complications (0.8% incidence of O_2 Sat <95%) [46]. Others have suggested that ketamine may be an alternative for sedation and analgesia during colonoscopies and liver biopsies, where upper airway stimulation is minimal [49]. The role of safe ketamine in pediatric colonoscopy has yet to be fully explored.

Nitrous Oxide

Nitrous oxide is an inhalational gaseous mixture which has analgesic, sedative, and amnestic properties. It is generally prepared as 50% nitrous oxide in oxygen, and is a short-acting agent with rapid onset of action (3–5 min) and short duration of effects after withdrawal (3–5 min). Several studies

have suggested that nitrous oxide may provide rapid and effective sedation for children undergoing gastrointestinal procedures, without inducing deep sedation [50, 51]. Comparisons with midazolam and fentanyl combinations suggest that nitrous oxide may not provide enough analgesia for colonoscopy [51]. Nitrous oxide may be adequate for endoscopy and rectosigmoidoscopy, two less painful and stimulating procedures.

Diprivan (Propofol)

Propofol may be administered during pediatric endoscopy either as a total intravenous anesthetic or in combination with inhalational agents. Propofol, alone or in combination with other agents, has been shown in multiple studies to be highly effective at inducing sedation in children who are undergoing both upper and lower endoscopy, and provides excellent amnesia for the procedure [52–55].

Propofol is an ultra short-acting anesthetic that features both a rapid onset of action and a short recovery time. It can be used to induce and maintain a spectrum of sedation levels, as well as to achieve anesthesia. Children who receive propofol have shorter induction times than children who received midazolam and fentanyl. Nevertheless, this faster induction time has not been shown to improve procedural efficiency in pediatric endoscopy units [56].

A pharmacologic disadvantage of propofol is its relatively narrow therapeutic range. Pharmacokinetic studies of children who received propofol demonstrate that average total propofol doses per kilogram of body weight to achieve targeted plasma propofol concentrations are higher in younger children [57, 58]. Propofol can be given alone or in combination with other sedatives. Elitsur et al. reviewed propofol sedation for endoscopic procedures in children and found that a lower propofol dosage was needed when propofol was given in combination with midazolam and fentanyl, than when propofol was given alone. Propofol conferred amnestic effects, independently of those conferred by midazolam [59].

Titrating propofol to achieve sedation without inducing general anesthesia requires clinical expertise and, even when administered by anesthesiologists, carries the risk of an inadvertent anesthetic. Kaddu et al. reported that 20% of pediatric patients receiving anesthesiologist-administered propofol for upper endoscopy experienced transient apnea [53]. A recent study demonstrates that a slow administration of propofol (over 3 min) confers less respiratory depression than more rapid delivery [60]. Given its high potential to induce respiratory depression and cardiovascular instability, propofol is often routinely administered by anesthesiologists for pediatric endoscopy [53, 55, 61].

Non-Anesthesiologist Administered Propofol Sedation (NAAPS)

NAAPS is an acronym used to describe the administration of propofol under the direction of a physician by an appropriately qualified registered nurse or physician who has not been trained as an anesthesiologist [62]. Propofol may be used either alone or in combination with one or more other agents, and a level of moderate-to-deep sedation is targeted [63, 64]. NAPS or Nurse-Administered Propofol Sedation refers to the first model used for nonanesthesiologist-administered propofol, and generally implies propofol administration by a registered nurse.

Propofol administration by nonanesthesiologists is an off-label use as its package insert identifies it as an anesthetic agent. The off-label use of propofol in NAPS and NAAPS has raised safety and liability questions for nurses, gastroenterologists, and facilities. In some states, registered nurses have maintained authority to refuse to administer sedation if they deem it to be unsafe. For example on 13 October 2005, the Minnesota Board of Nursing issued a Statement of Accountability for Administration of Medications Classified as Anesthetics by the Registered Nurse. It classified propofol as a sedative hypnotic at lower doses and gave the nurse the authority to "decline to administer medications classified as anesthetics or other medications if the registered nurse perceives the administration would be unsafe under the circumstances" [65].

Along these lines, one training syllabus for a GI-delivered NAPS manual begins with the following: "STOP! Do you need to do this patient's procedure now? Is this the time that is optimal for the patient's safety? Are all of your rescue systems and components ready? Are your rescue skills adequate? Does this patient need sedation, light sedation, varying levels of sedation or deep sedation? Are team members rested, relaxed, and attentive? Is this a case for which you should have an anesthesiologist?" [66].

In 2007, it was estimated that over 150,000 adult patients had received NAAPS for endoscopy [67]. To date, this number is approaching 600,000 patients, with morbidity and mortality cited as comparable to more traditional IV sedation regimens [62].

Table 14.5 Propofol matrix[a]

Initial propofol dose (mg)	ABL1 (mg)	ABL2 (mg)	ABL3 (mg)
20	0	5	10
30	5	5–10	10–20
40–60	5	5–10	10–20
70–110	10	10–20	20
120–160	10	20	20–30
160–200	20	20–30	40–60
200–300	20–30	30–50	50–70

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ABL adverse body language level

[a]This matrix is an example of a propofol algorithm for adults. Subsequent propofol doses are based on the initial dose and the patient's current ABL score. This matrix represents the algorithm designed by Dr. John Walker, the publication of which does not imply endorsement

NAAPS for Adults: Could the Algorithms Apply to Children?

When considering a possible role for NAPS or NAAPS in pediatric gastroenterology, it is important to recognize that the induction dose regimen for NAPS-delivered propofol was designed for the sedation of adults greater than 12 years of age only. There have been no publications regarding the use of NAPS or NAAPS solely intended for pediatric gastrointestinal procedures. A review of the strategies and regimens applied to adults may guide sedation care providers in the potential application of NAPS or NAAPS to pediatric use.

The Propofol Matrix (Table 14.5) represents one model for guiding dosing in response to clinical cues and seeks to address the perceived need among adult gastroenterologists for more clearly defined algorithms [68, 69]. As with all published references for NAPS, the Propofol Matrix has been designed for use in adults, and relies on assessments of patient responsiveness, both purposeful and nonpurposeful physical and verbal responses to guide propofol dosage. These responses are graded on a scale of 1–4, and referred to as Adverse Body Language (ABL) Levels.

In the Propofol Matrix, ABL 1 Level describes a patient who exhibits slight contraction of proximal limb flexors, mild grimacing, and low volume verbalization. Moderate limb movement and verbalization at normal conversation volume constitutes Level ABL 2. A loud outburst, "perfectly spoken" sentence or purposeful body movement describes ABL 3. "Restless leg syndrome" movements, flapping of hands, and slight body twitching are generally not used for ABL scoring and do not affect dosing decisions. Each person has an ABL goal identified prior to the start of the procedure, and this level may differ between patients and procedure, taking into account the patient's medical condition and the procedure itself. In clinical applications, the ABL score should augment assessments of ventilation.

In adults, the initial dose of propofol is given in milligrams and calculated using the formula (100 – age) up to a maximum of 60 mg. All initial doses are given as a single bolus. The first dose represents "Time Zero," the second dose is given at 60 s, and subsequent doses are administered every 30–40 s. The level of sedation is closely followed by the sedation team and the ABL level is used to determine subsequent, appropriate dosing strategy.

There are a number of published studies of large numbers of patients that support the efficacy and safety of NAAPS. A prospective cohort study of 27,061 adult patients in two ambulatory GI settings presented NAAPS data for administration by an endoscopy nurse and supervised by

the endoscopist. Monitoring consisted of pulse oximetry and clinical assessment. The mean dose of propofol for EGD was 161 mg (range 50–650 mg). The mean dose of propofol for the colonoscopy was 116 mg (range 30–500 mg) in addition to 25 mg of meperidine. Oxygen saturation fell below 90% in 2.3% but normalized within 30 s of stimulation and increased oxygen delivery via nasal cannula. Six patients (ASA III) required brief positive pressure, airway assistance for less than 30 s [70]. This study suggests that a GI endoscopist with a specialized team consisting of one physician endoscopist and one endoscopy nurse may be able to administer propofol sedation with pulse oximetry and vigilant attention [71].

NAPS was used for 9,152 adult endoscopies in an ambulatory surgery center. Registered nurses, under the supervision of an endoscopist or gastroenterologist, described seven cases of respiratory compromise of which none required endotracheal intubation. 5/9,152 required positive pressure ventilation via face mask. On average, patients were discharged within 18 min of completing the procedure [72].

Rex et al. presented the outcomes of 36,743 cases of NAPS administered at three endoscopy centers. The incidence of respiratory compromise was not statistically different between centers, ranging from <1:500 to <1:1,000. There were no cases of death or endotracheal intubation [73].

Worldwide, endoscopists-directed propofol (EDP) administration is being practiced by some as a substitute for anesthesia specialists. 646,080 records from around the world were reviewed. The incidence of positive pressure mask ventilation was 0.1%. Eleven cases required endotracheal intubation and there were four deaths. The deaths occurred in two patients with pancreatic cancer, one who was severely developmentally challenged and one with severe cardiomyopathy [62].

To date, there is no such widespread, global adoption of NAPS for children. In fact, there are no published pediatric NAPS studies. A recent prospective study used NAAPS in children with a protocol of 1–2 mg/kg of propofol induction dose followed by 0.5–1.0 mg/kg supplements as needed. Propofol was administered by pediatric residents to 716 children for 811 procedures. The residents had been trained in cardiopulmonary resuscitation and had completed a 4-week training period during which they had performed bag-mask ventilation and endotracheal intubation a minimum of 20 times. There were careful selection criteria for suitable sedation candidates. Children were ASA I and ASA II only. Those with any indication of airway obstruction (existing or potential), respiratory disease, seizures, or risk of aspiration were excluded. Overall there was a 0.7% (6/811) incidence of positive pressure ventilation, brief oxygen desaturation in 12%, and no occurrence of endotracheal intubation [70].

Because of its high reliability as a safe, effective, and efficient sedative, propofol, as administered by anesthesiologists in a dedicated endoscopy unit, separate from the operating room, has emerged as an attractive option for pediatric gastrointestinal procedures [53, 74–76]. A growing number of pediatric gastroenterologists are using, or planning to use, propofol in their own practices, almost entirely with the assistance or supervision of an anesthesiologist [5]. Recruiting anesthesiology assistance to the endoscopy unit will decrease the need for operating room time and should facilitate the scheduling of procedures.

Monitoring of Children Undergoing Endoscopic Procedures with Sedation

The sedation of children for endoscopy requires a carefully coordinated team of physicians and nurses [30, 77]. In general, any evidence of poor ventilation – either by visual assessment or from physiologic monitors (pulse oximetry, precordial stethoscope, capnography) – should trigger immediate intervention.

Patient Positioning

All patients undergoing diagnostic upper and lower endoscopic procedures with sedation should

be placed in the left lateral decubitus position to avoid the supine position with its accumulation of secretions in the oral pharynx and associated risk of upper airway obstruction or laryngospasm. Patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) may require the prone or prone-oblique position. Obviously, airway monitoring, access to the airway, and management of complications (i.e., airway obstruction, laryngospasm) are more challenging in the prone position.

Pulse Oximetry

Visual and clinical assessments are important adjuncts to physiologic monitoring for ensuring patient safety. Oxygen desaturation represents an objective means of detecting inadequate respiration in children. Suboptimal ventilation by clinical assessment may be missed or overlooked but will be identified by pulse oximetry. Oxygen desaturation tends to be a relatively late sign of suboptimal ventilation [78]. Supplemental oxygen during upper GI endoscopy has been shown to decrease the incidence of desaturation (<92% for greater than 15 s) which occurs [79].

Capnography

The limitation of pulse oximetry during endoscopy is that patients may be well saturated with coincident significant apnea and carbon dioxide retention. At some centers, precordial stethoscopes, visual inspection, and palpation are used to supplement the monitors. Compact microstream capnographs using aspiration flow technology allow the accurate real time electronic graphic display of ventilatory waveforms in nonintubated patients by measuring their end-tidal carbon dioxide [78, 80].

Microstream capnography has been shown to provide a highly reliable measurement of abnormal ventilation [80]. Employing capnography in the pediatric endoscopy setting may reveal that abnormal ventilation is occurring during procedures in children at rates higher than expected [81]. While no studies have compared capnography with palpation of the breath, one randomized controlled trial of children undergoing endoscopic procedures demonstrated capnography to be more effective than direct visualization at identifying patient hypoventilation [82]. Endoscopy staff documented poor ventilation in 3% of all procedures and no apnea, while capnography indicated alveolar hypoventilation in more than half, and apnea during a quarter of procedures [82]. Integrating capnography into patient monitoring protocols both in adult and pediatric endoscopy settings may ultimately improve the safety of nonintubated patients receiving moderate sedation. Recent multi-society guidelines published by the American Gastroenterological Association (AGA) Institute, the American Society of Gastrointestinal Endoscopy (ASGE), and the American College of Gastroenterology suggest that capnography may become a standard for patient monitoring [83].

Rescue Equipment for Sedated Gastrointestinal Procedures in Children

Emergency rescue equipment should be immediately and easily accessible in all gastrointestinal procedure rooms. In addition to pharmacologic agents, airway equipment is essential, in particular, all sizes of laryngeal mask airways and endotracheal tubes, bag valve masks for delivering positive pressure ventilation, laryngoscopes, nasopharyngeal and oropharyngeal tubes, and dedicated suction. In an emergency, the gastroenterologist should be trained if administering deep sedation to rescue from an anesthetic [12, 84, 85].

The Future Direction of GI Sedation

As propofol grows in popularity among gastroenterologists, so does interest in developing sophisticated intravenous delivery systems capable of integrating patient data into computerized programs to guide drug delivery. This delivery system has been denoted as CAPS or "Computer-Assisted Personalized Sedation." The

goal of CAPS is to provide moderate sedation, with patients still able to respond to verbal or tactile instructions. Initial CAPS outcome data in adult patients undergoing gastrointestinal endoscopy appears promising. One thousand adults (ASA I–III) underwent upper or lower GI endoscopy with either a CAPS system or a combination of benzodiazepines and opiates. Sedation depths were similar between groups although those who received CAPS had less oxygen desaturation, less adverse events, and faster recovery. CAPS received high satisfaction scores from both patients and endoscopists. Postprocedure assessments by anesthesiologists generally agreed with clinically significant decisions made by the CAPS device [86].

Current Status of Sedation Among Pediatric Gastroenterologists

With the recent awareness of manpower shortages in anesthesia, nonanesthesiologists continue to search for safe alternatives to anesthesia-delivered sedation for endoscopy [87]. Pediatric sedation for gastrointestinal procedures carries its own unique considerations and risks. The safety, efficacy, and application of nonanesthesia-delivered propofol for pediatric endoscopy have yet to be fully examined. Over time, with CAPS and the growing recognition of the advantages of using propofol for gastrointestinal procedures, pediatric endoscopists may ultimately add NAAPS to their sedation options.

Case Studies

Case 1

A 15-year-old, 5′ 5″, 55 kg teenager with a known diagnosis of ulcerative colitis requires colonoscopy to evaluate the efficacy of her medical regimen. After discussion with the patient, it is decided to use moderate sedation with a midazolam/fentanyl regimen to perform the procedure. The patient is anxious upon arrival in the endoscopy unit, and is offered a dose of oral midazolam (10 mg) prior to placement of the intravenous line. Approximately 20 min after the po midazolam, the IV is placed successfully and the patient is brought to the procedure room and placed in the left lateral decubitus position. A dual-purpose nasal cannula is placed in the nares to allow a baseline 2L NCO_2 to be administered and capnography to be monitored. Topical lidocaine jelly is applied to the anal canal. The patient is administered two doses of midazolam (2 mg each) every 3 min and two doses of fentanyl (50 μg each) every 5 min in a step-wise fashion, titrating to effect. The patient is able to open her eyes with verbal command, but is comfortable for the procedure to begin.

Case 2

A 15-year-old with history of gastroesophageal reflux disease presents for an upper endoscopy. It is noteworthy that he is 6′ 4″ and weighs 265 pounds and has a body mass index (BMI) of 32.4.

Considerations in evaluation and triage of this patient for office-based sedation include the BMI, the airway, and aspiration risk. In adults, a BMI of greater than 45 generally excludes nonanesthesia-delivered sedation. In children and adolescents, BMI risk factors differ by age and a BMI <45 may pose a risk. This boy had a BMI of 32 and had an Airway Assessment (Table 14.2) of zero. Regardless, vigilance and anticipation of airway obstruction, laryngospasm, coughing, and apnea were implemented and discussed prior to the sedation. Of interest, younger patients are noteworthy for spontaneous rapid and sweeping movements of the right arm (in the left lateral decubitus). Care must be taken to avoid this arm from being injured by a metallic object (arm rail, C-arm) in the patient's environment. NPO status must be verified, confirmed, and then renewed a final time: children and

adolescents are prone to inadvertently or surreptitiously violate the NPO guidelines either with or without their parent's knowledge. Undigested debris must be anticipated in the stomach or esophagus, particularly in the younger age groups. This patient underwent NAAPS and received 250 mg propofol for the short procedure which diagnosed Grade A erosive esophagitis.

Case 3

A 3-year-old boy with cerebral palsy, contractures of all four extremities, marginal oral aperture, and constant vomiting/regurgitation presents for upper endoscopy. He has a very poor muscle mass and greatly impaired cognition. This case was evaluated by the endoscopist and determined to be inappropriate for NAAPS because of the risk of aspiration with an unprotected airway and sedation. An anesthesiologist assumed responsibility for his care and illustrated the salient teaching points which warranted anesthesia management [88]. The anesthesiologist and endoscopist performed a physical exam and careful airway assessment together. It was assumed that regardless of NPO status, this patient would not have an empty stomach (25 cc/pH 2.5 or greater). Rapid acquisition and securing of the airway with an endotracheal tube was planned. Succinylcholine would usually have been chosen for rapid neuromuscular blockade and subsequent intubation. However, because of the risk of hyperkalemia in this patient who was being evaluated for myopathy, a nondepolarizing muscle relaxant was chosen over succinylcholine. A shoulder roll improved visualization of the vocal cords along with head extension in the sniffing position. Advanced airway skills to secure the airway should be anticipated in this patient with limited mouth opening supplemented with the availability of alternative airway devices (laryngeal mask airways, video laryngoscopes, fiberoptic bronchoscopes).

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Sedation in the Emergency Department: A Complex and Multifactorial Challenge

15

Robert M. Kennedy

*The Wand is only as good as the Wizard**

Introduction

Why Procedural Sedation and Analgesia?

Painful therapeutic procedures are frequently necessary during emergency care of children, many of whom already have a painful and frightening injury or illness. Immobility for diagnostic radiological procedures in young children is also often required. These procedures are distressful for the children, their parents, and their healthcare providers. Inadequately relieved procedure-related pain and distress produces physiological and psychological reactions that have acute and long-term consequences [1–6].

Safe and effective management of procedure-related pain and anxiety in the emergency department (ED) has become expected [7]. It facilitates controlled accomplishment of therapeutic and diagnostic procedures [3, 8, 9], reduces psychological trauma and its sequelae [3, 5, 8, 10], reduces healthcare provider and parental distress, and improves parental acceptance of rendered care [11]. Many advances in procedural sedation and analgesia (PSA) for nonelective procedures in non-fasted patients in the ED have occurred over the past 20 years as a result of intense interest in this concept and the development of general and pediatric emergency medicine specialties, for whom PSA is now considered core training [12]. Family and third-party payer's desire for definitive management of acute injuries during initial ED visits also seems to be increasing. This chapter reviews some of the PSA techniques shown to safely and effectively decrease children's pain and anxiety associated with procedures in the ED. Since pain and anxiety are frequently indistinguishable, the combination will often be referred to as distress.

Long-Term Negative Impact of Painful Procedures

Elimination or relief of pain and suffering, whenever possible, is an important responsibility of physicians caring for children [13], as unmanaged pain can result in a variety of negative long-term consequences [14]. Accumulating evidence indicates that by the middle of the third trimester of human gestation, ascending pain fibers fully connect to the primary somatosensory cortex of the brain [15, 16]. Descending inhibitory pain pathways, on the other hand, appear to require postnatal development. Rather than being less sensitive to pain, young infants may actually experience pain more intensely than older children [17]. As the brain rapidly matures during the first weeks to months after birth, recurrent painful

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stimuli may alter the formation of new neuronal circuits, resulting in children's hypersensitivity and increased behavioral response to noxious stimuli [15, 18–23].

Inadequately controlled procedure-related pain has been correlated to increased distress and maladaptive behaviors during subsequent healthcare interactions. Boys circumcised at birth without effective anesthesia had increased distress at their 4- and 6-month routine vaccinations compared to uncircumcised controls [24]. Similarly, toddlers who had painful postoperative care during the first 3 months of life demonstrated greater pain responses at their 14-month immunizations compared with controls [25]. In older children, painful therapeutic procedures have been associated with negative memory and greater pain during similar future procedures [26–28], even when those future procedures are performed with adequate analgesia [5]. Although the mechanisms underlying these observations have yet to be fully elucidated, these studies show that painful episodes can be encoded into children's implicit and explicit memories [23]. While praising a child following a painful procedure, in an effort to modify negative memories, may lessen these memories and reduce distress during subsequent procedures [29], prevention of negative memories by employing effective sedation-analgesia for intensely painful procedures is likely a crucial part of preventing the negative feedback loop that can then cause greater anxiety and pain during future procedures and healthcare interactions [30, 31].

When May PSA Not Be Needed?

PSA requires substantial and frequently scarce healthcare resources in a busy ED and has significant, albeit rare, risks. Emergency healthcare providers therefore increasingly are employing strategies that provide effective minimally painful techniques for local anesthesia or systemic analgesia. Combined with psychological or behavioral approaches to reduce patient anxiety, these strategies may greatly reduce the need for PSA as well as diminish the need for deeper sedation [32].

Nearly Painless Local Anesthesia

Topical Anesthetics

Use of topical anesthesia for children's lacerations has become standard in many EDs. Locally compounded solutions or gels containing 4% lidocaine, 0.1% epinephrine (adrenaline), and 0.5% tetracaine (LET or LAT), provide local anesthesia when instilled for 20–30 min into an open wound or abscess [33–35]. These solutions are more effective in scalp and facial lacerations than those on extremities or the trunk but their initial use markedly reduces the pain of subsequent injection of lidocaine, if such is needed. Careful application of limited amounts of these solutions onto lip or mucous membrane lacerations, e.g., using a cotton-tip swab, has been shown safe and can be quite effective [36]. Caution must be used, especially in small children, as rapid absorption of the anesthetics could cause toxicity. A recent study also found use of LET on finger lacerations safe and effective [37].

Buffering Injected Lidocaine

Pain associated with injection of lidocaine can be markedly reduced by buffering the anesthetic, injecting slowly through fine needles (e.g., 30-gauge) subcutaneously instead of intradermally, and warming the anesthetic to body temperature [38–42]. Buffering lidocaine, with or without epinephrine, to pH 7.0–7.2 by mixing 1 part of 1 mEq/mL sodium bicarbonate with 9–10 parts of 1% lidocaine markedly decreases the pain of injection [43, 44]. Buffering also decreases onset time for anesthesia [44] without affecting efficacy or duration [44–46]. The buffered mixture is stable for at least 3 weeks when stored at room temperature [45] and longer when refrigerated [47].

Psychological Interventions Reduce Distress and Need For PSA

Acute injury or illness causes significant anxiety and stress for most children and their parents. Lack of understanding of ED routines for care,

ongoing pain, prolonged waits, preconceived notions about emergency care, and numerous other known and unknown factors interfere with effective preparation of the child and use of the child's and parents' coping mechanisms [48]. Consequently, many young children are frightened and unwilling to cooperate with necessary procedures, even when little or no pain is involved. A warm smile and a slow respectful and sometimes playful approach may reduce the frightened child's perception of the provider as a threat and increase the likelihood of cooperation without need for sedation. Addressing parental concerns and providing them with an explanation of the plan for care, along with age-specific suggestions on how they can allay some of their child's fears and anxieties, allows them to prepare their child as well as themselves.

Having their parent at their side during painful procedures in the ED is of utmost importance for school-aged and younger children, despite realizing their parent can do little to alleviate procedural pain [49]. Parents likewise believe their presence during procedures is important and beneficial to their children [50–52]. EDs increasingly are enacting policies to give parents the option of staying with their child during all procedures and resuscitations, usually with a staff member dedicated to explain the care provided and to monitor the parent for signs of extreme distress, syncope, etc [53–55]. When suggestions are given to parents on how to help their child, e.g., touching, distracting with stories, reciting the alphabet, counting, etc, parents can provide significant assistance in accomplishing anxiety provoking procedures without sedation [56, 57]. In addition, nonthreatening language should be used to characterize anticipated sensations, e.g., "freezing, poking, or squeezing" instead of "burning, bee sting, or hurting." Simply allowing young children to sit in their willing parent's lap, with parents providing distraction and hugs for mild restraint, markedly reduces the child's distress during minor procedures [58]. Combining this technique with L.E.T. for topical wound anesthesia, supplemented as needed with buffered lidocaine injected via a 30 gauge needle, the author rarely finds it necessary to employ PSA for suturing lacerations in young children.

What Makes ED PSA Different?

Children often exhibit significant distress when faced with ED procedures despite administration of analgesic medications and psychological interventions. They may be anxious about sounds and sights they do not understand, fearful because of prior experience or hearsay, or in pain because of incomplete analgesia or local anesthesia. Furthermore, their usual coping mechanisms may be in disarray because of the unexpected nature of their illness or injury and their perception that they have no control over the impending treatment. When children refuse or are unable to cooperate with necessary procedures or if effective local anesthesia is not possible, safe and effective pharmacologic sedation can avert detrimental patient, parent, and practitioner sequelae and facilitate accomplishment of the procedure [5, 59, 60].

ED PSA in children, however, has greater inherent risks when contrasted to elective sedation. Patients frequently have not fasted for traditional periods and consequently may have "full stomachs" [61–63]. Postponement of procedures to allow fasting in the ED may be impractical due to limited resources. More importantly, postponement to allow gastric emptying is likely ineffective because painful injuries and serious illnesses unpredictably delay emptying of stomach contents; moreover, necessary administration of opioids for pain management likely exacerbates this problem. Compounding these issues, children undergoing painful or anxiety provoking procedures typically require deeper levels of sedation than adults or teenagers who may be able to better control their behavior [1]. Unanticipated arrival or deterioration of other ED patients and overextended ED staff may result in the sedating physician unpredictably being pulled away or distracted by other patients' emergencies. Finally, therapeutic procedures performed by trainees in academic EDs frequently are more prolonged and require longer periods of sedation.

Deciding Whether to Perform PSA

The first and foremost goal of pediatric PSA is assurance of the patient's safety and welfare during the sedation and recovery. With this in mind and the limitations noted earlier, the clinician considering PSA must carefully consider the following:

1. *Is the procedure necessary?* Some procedures that would require PSA in many children may be unnecessary. For example, it is likely that, as in adults, many lacerations of the hand and feet heal as well with bandaging as with suturing [64]. Similarly, virtually all tongue lacerations heal well without suturing [65].
2. *Do I have the resources and skills to rescue if rare but serious adverse events occur?* For example, would I be able to administer a paralytic drug for severe laryngospasm or secure the airway by intubation?
3. *What if an unexpected patient with a critical emergency arrives?* Do I have the resources to continue the PSA and procedure? Or, if I had to leave the patient, do I have the resources to safely recover the patient?

Systematic Approach to Safe ED PSA

Goals of PSA

Pediatric PSA by experienced providers has inevitable risks of adverse events including respiratory depression, apnea, airway obstruction, vomiting, hypotension, and dysphoria [66]. The first and foremost goal of pediatric PSA is assurance of the patient's safety and welfare during the sedation and recovery [59, 67]. Within this context, additional goals include control of behavior (muscle relaxation or relative immobility) and minimization of procedure-related pain, anxiety, memory, and negative psychological responses [59]. Safe attainment of these goals requires careful patient screening for factors associated with increased sedation-related risk of adverse events or difficult airway management, preparation for management of possible adverse events, and meticulous assurance of effective patient cardiopulmonary and other vital functions during and after the procedural sedation.

By developing a routine or systematic approach for ED PSA, the emergency physician reduces risks for the patient by identifying children at increased risk of adverse events and increasing preparedness for safe and effective management of adverse events, should they occur [68]. The systematic approach should include the following steps:

1. Pre-sedation patient assessment
2. Informed consent
3. Plan for sedation
4. Documentation/sedation record
5. Recovery/discharge
6. Quality improvement

1. *Pre-sedation patient evaluation and risk assessment*: Children should be screened for factors that may be associated with increased risk of adverse events or difficult management of these events during sedation. Identification of these risks allows for better preparation for management of untoward events or development of alternative plans to reduce the likelihood of undesired effects. In addition to general sedation screening in preparation for an ED procedure, a focused physical exam immediately prior to sedation should be repeated to detect any acute changes in the child's physiological status such as acute onset of wheezing or fever.

   Pre-sedation *history and physical examination* should focus upon the patient's cardiorespiratory status and airway to determine the sedator's ability to rescue breathe for this individual, if necessary [59, 69, 70]. A focused history may be guided by the mnemonic *AMPLE*:

   (*A*) Allergies to medications, latex, CT contrast, food (e.g., egg allergy prohibits use of propofol, shellfish allergies are associated with CT contrast reactions)

   (*M*) Current Medications or illicit drugs that might interact with PSA medications; these often reveal concurrent diagnoses that may impact PSA choices, e.g., psychiatric medications

(*P*) Past medical history, including any complications with sedation or anesthesia and chronic illnesses; history of snoring/stridor, recent URI/respiratory infections or asthma exacerbations, GERD, cardiac history, prematurity, any neuromuscular disease (may contraindicate succinylcholine), and history of airway surgery/tumors/malformations

(*L*) Last meal/fluid intake

(*E*) Events leading to need for procedure, e.g., associated injuries

(a) ASA physical status classification

The patient physical status classification endorsed by the American Society of Anesthesiologists (ASA) [71] to predict risk for adverse events during general anesthesia [72, 73] is helpful in assessing sedation risks and is summarized in Table 15.1. ASA Class I and II children are at low risk for serious adverse events when carefully monitored. Events which are initially minor, such as upper airway obstruction during deep sedation, usually can be easily addressed with simple interventions and catastrophic sequelae prevented. However, children with underlying illnesses often have less cardiopulmonary reserve and thus a greater risk for adverse responses to sedative and analgesic medications and their rescues often are more difficult and complex. Therefore, when possible, it is suggested an experienced sedation provider or anesthesiologist be consulted for planning sedation of ASA Class III patients and an anesthesiologist consulted for Class IV or V patients.

(b) Airway assessment: comorbid risk factors, Mallampati classification

Factors associated with difficulty in airway management include those that make it hard to visualize the larynx or partially or completely obstruct the upper airway. Examples include: history of previous problems with anesthesia or sedation including prolonged intubation or unplanned hospitalization, stridor, snoring, or sleep apnea, chromosomal abnormality (e.g., Trisomy 21), history of prematurity with prolonged intubation, significant obesity, short neck or limited neck mobility, receding mandible (small lower jaw) or decreased hyoid-mental distance, dysmorphic facial features (e.g., Pierre–Robin syndrome), small mouth opening, protruding incisors, loose teeth, dental appliances, high, arched and narrow palate or history of cleft palate repair, large tongue, tonsillar hypertrophy, or no visible uvula (Fig. 15.1 Mallampati airway classification III, IV) [69, 70].

Problems associated with increased risk of adverse events and for which consultation

Table 15.1 ASA physical status-E classification [71]

Status	Disease state
I	No organic, physiologic, biochemical, or psychiatric disturbance
II	Mild to moderate systemic disturbance that may or may not be related to the reason for procedure, e.g., *mild asthma, well-controlled diabetes, controlled seizure disorder, anemia*
III[a]	Severe systemic disturbance that may or may not be related to the reason for procedure, e.g., *heart disease that limits activity, poorly controlled essential hypertension, diabetes mellitus with complications, chronic pulmonary disease that limits activity, poorly controlled seizure disorder*
IV[b]	Severe systemic disturbance that is life-threatening with or without procedure, e.g., *advanced cardiac, pulmonary, renal, endocrine or hepatic dysfunction, e.g., severe bronchopulmonary dysplasia, sepsis*
V[b]	Moribund patient who has little chance of survival but is submitted to procedure as a last resort (resuscitative effort), *e.g., septic shock, cerebral trauma, pulmonary embolus*

"E" is added to indicate a nonelective or emergent procedure, e.g., ASA I–E

[a] Consultation with experienced sedation provider or anesthesiologist encouraged

[b] Consultation with anesthesiologist strongly encouraged

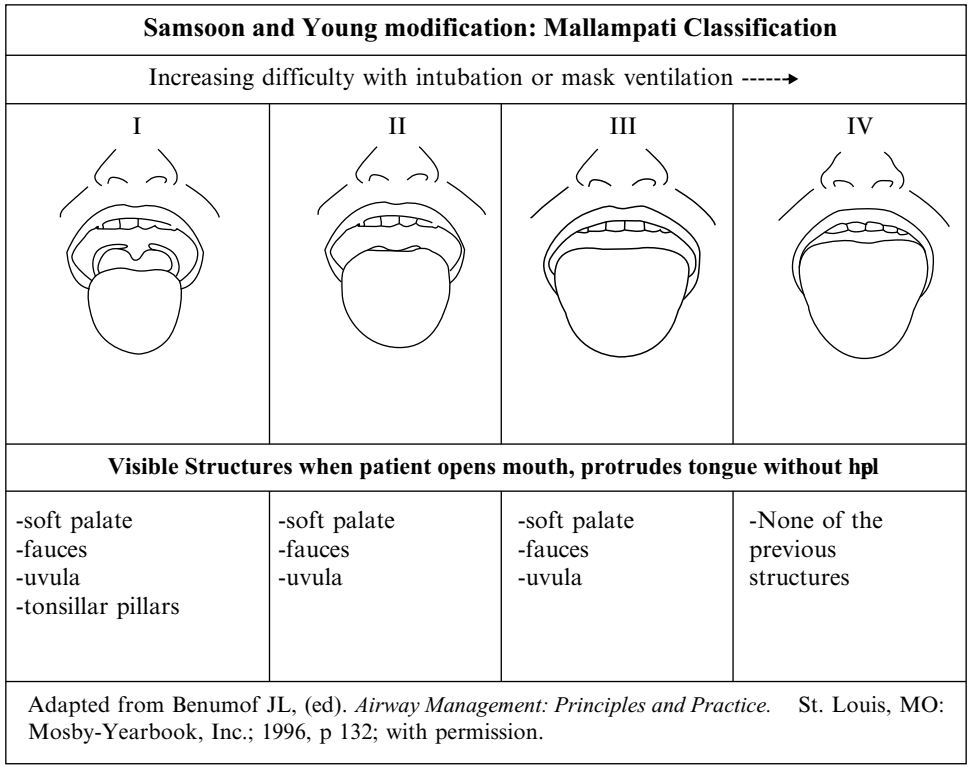

Fig. 15.1 Mallampati airway classification (adapted from Benumof [360]; with permission)

with an experienced sedation practitioner or anesthesiologist is suggested include: [74]

- ASA physical status III or IV
- Current upper respiratory illness (URI)[1]
- Pulmonary: wheezing not cleared by a bronchodilator, obstructive sleep apnea
- Morbid obesity (>2× ideal body weight)
- Cardiovascular conditions: cyanosis, congestive heart failure
- Neurological conditions: poorly controlled seizures, central apnea
- Gastrointestinal conditions: uncontrolled gastroesophageal reflux
- Prematurity with residual pulmonary, cardiovascular, gastrointestinal, neurological problems
- Age <3 months
- Pregnancy or suspected pregnancy
- Neuromuscular disease
- Severe developmental delay
- Patients who are difficult to control
- History of failed sedation, over-sedation, or paradoxical response to sedatives

Screening for acute illness: Patients should be screened for acute illnesses that may increase their risk for sedation-related adverse effects. When acute illness is detected, the sedation provider must weigh the increased risk against the need for the diagnostic or therapeutic procedure.

(c) *Fasting status and risk of aspiration*. To decrease the risk of pulmonary aspiration of gastric contents in healthy children undergoing general anesthesia for elective

[1] Note: Upper respiratory illness (URI) may increase the risk of laryngospasm, bronchospasm, and hypoxia during sedation. Mild URI symptoms alone (non-purulent rhinitis, afebrile, cough that clears) may not be an indication to cancel PSA but management should reflect anticipation of above potential complications. Severe URI (febrile, purulent discharge, wet cough) should prompt consideration of cancelation of non-emergent or urgent procedures.

procedures, fasting from clear liquids a minimum of 2 h and from milk or solid food 6–8 h is a well established consensus-based practice [75]. However, as noted in these guidelines, "Published evidence is silent on the relationship between fasting times, gastric volume, or gastric acidity and the risk of emesis/reflux or pulmonary aspiration in humans." In two more recent reviews of the literature examining whether children should undergo fasting prior to ED PSA [76, 77], it is noted that little clinical data has been published to help answer this question. It is difficult to extrapolate directly to PSA from the long experience with safe general anesthesia. It is likely that risk of aspiration is less during ED PSA compared to general anesthesia in the operating room for several reasons. First, protective airway reflexes are generally preserved at the depth of moderate sedation [69, 78]. Second, airway reflexes are also relatively intact during sedation with the commonly used dissociative agent ketamine during deep sedation or even light general anesthesia [79]. Of concern, however, these reflexes are likely blunted during deep sedation with opioids, benzodiazepines, barbiturates, propofol, and etomidate, especially if sedation is deep enough to cause apnea [77]. Third, intubation of the trachea, rarely performed in children undergoing ED PSA, likely increases the risk of pulmonary aspiration due to pharmacological abolition of protective reflexes to facilitate intubation and mechanical interference with these reflexes during passage of the endotracheal tube into the trachea [72, 73, 80]. Fourth, the great majority of children receiving ED PSA meet ASA physical status class I or II criteria [9, 61–63, 78, 81] and, compared to those in ASA physical status classes III and IV, are associated with less risk of adverse events during anesthesia [72, 73]. It is the combination of these differences, i.e., moderate sedation, common use of dissociative ketamine for deep sedation, lack of manipulation of the larynx, and healthy patients, that likely results in ED PSA having lower risk of aspiration compared to general anesthesia.

A more robust literature on identification of risk factors for aspiration in children undergoing general anesthesia has found no benefit from routine preoperative administration of antacids or pharmacological agents to increase gastric motility [75, 82]. Gastric fluid volume or pH were not different with NPO periods of 2, 4, and 12 h after drinking apple juice in one study [83] or after 30 min to 3 h, 3–8 h, or more than 8 h after clear liquid ingestion in another trial [84]. No studies have examined gastric emptying in children after solid intake but one small study of adult women after a light breakfast found 3 of 8 had emptied their stomachs by 2 h and all by 6 h [85].

The incidence of pulmonary aspiration during ED PSA is uncertain but appears to be very low. In a literature review of adverse events during ED PSA [76], after combining studies with a total of 4,814 children, clinically apparent aspiration during PSA was reported in only 1 account of 2 children, both of whom had fasted standard NPO periods and did not appear to be ED patients. These patients were deeply sedated with opioid-barbiturate combinations which blunt airway reflexes, one for a radiological procedure and the other for bronchoscopy. Both required only supplemental oxygen and observation [68]. In nearly 50,000 elective propofol-based sedations, 4 children were noted to have aspirated; all recovered without sequelae after positive-pressure ventilation and supplemental oxygen, and were discharged the day of or day after the procedure [86]. The incidence of aspiration in more than 100,000 children undergoing general anesthesia has been reported to be 1:978 and 1:2,632 patients by Warner [72] and Borland [73]. During emergency surgery, aspiration occurred as frequently as 1:373 patients in the Warner study [72]. Although only a rough estimate, pooling of the available data in the literature

suggests the incidence of clinically apparent pulmonary aspiration during ED PSA is no more frequent than 1:2,000 pediatric patient encounters [76]. Because of the rarity of its occurrence, much larger studies are needed to accurately estimate the incidence of aspiration, and any relationship with fasting, during ED PSA. For now, given the many variables present, clinical judgment has to weigh the risk and benefits for each patient [76, 77].

Vomiting, although not likely to result in aspiration when protective airway reflexes are intact, is a common adverse event during ED PSA in children, occurring in as much as 25% of patients, especially when opioids are coadministered prior to sedation [87, 88]. As supported by literature reviews [76, 77, 89], recent series of children receiving ketamine or nitrous oxide for ED PSA suggest there is poor correlation between the length of time of preprocedural fasting and vomiting [62, 63, 90]. No significant difference in frequency of vomiting was found between children fasted between 0, 2, 4, 6, 8, and greater than 8 h. This may be because the vomiting is medication induced and gastric contents have little effect on likelihood of vomiting.

Gastric emptying may also be unpredictably delayed in ill or injured patients due to development of ileus [91]. ED management of pain with opioids likely exacerbates this problem. Whether brief delay (1–6 h) of PSA decreases vomiting is undetermined. Coadministration of ondansetron has been found to reduce vomiting associated with ketamine-based ED PSA but only from 12.6 to 4.7% with 13 patients needing to be treated to prevent one episode of vomiting [92]. This and other strategies need further investigation. It is the practice of the author to consider all sedated ED patients to have "full stomachs" and to manage them with vigilance and preparation for assisting them in clearing their oropharynx by rolling them to their side or assisting them in leaning forward. Suctioning of the mouth is then used, if needed, to "mop up."

Pregnancy: Since many medications administered for ED PSA have the potential for causing harm to a fetus, it is recommended that the menstrual status be reviewed with post-menarchal girls and a urine pregnancy test performed prior to sedation. The United States Food and Drug Administration (FDA) has categorized medications based upon known or possible risk to a developing fetus as listed in Table 15.2. Increasing uterine size, greater tendency for vomiting, and many other changes also increase the complexity of PSA during pregnancy.

Table 15.2 United States FDA pharmaceutical pregnancy categories

Category A	Adequate studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category D	There is a positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

2. Informed consent
   The physician responsible for the sedation should provide to the patient and/or parents information concerning the objectives of the sedation, behavioral changes associated with the sedative regimen (especially important when the parent/guardian plans to remain with the patient during the sedation/procedure) and potential adverse effects during and after the sedation [59, 69, 93]. Parents should understand that, albeit rare, there is a risk of pulmonary aspiration, cardiopulmonary compromise, hypoxic brain injury, and/or death. *It is also recommended to discuss with them the possible need for muscle relaxation, intubation, hospitalization, and unsuccessful sedation with inability to perform the procedure*. These issues that have been discussed with the parent/guardian (and patient when appropriate) and that they have given their informed consent to proceed with the sedation, should be documented on the sedation record.

   Adverse effects/events generally discussed include:
   - Incomplete analgesia and/or amnesia
   - Respiratory depression/apnea
   - Pulmonary aspiration
   - Psychosis, recovery dysphoria
   - Catatonia/nystagmus
   - Dysrhythmias
3. Plan for sedation
   (a) *Selection of a medication plan*. Selection of medications and dosages should be guided by the desired key effect(s). An ideal regimen would provide acceptable analgesia, sedation and amnesia for residual awareness of procedure-related pain or anxiety, cause minimal adverse effects and work reliably with a wide therapeutic index, i.e., small differences in dose would not cause over-sedation or adverse events, have rapid onset and recovery, and be easy to titrate to effect. No single agent or combination of agents fully achieves these goals. Selection of procedural sedation medications therefore is based upon balancing desired effects with the potential for adverse effects. For procedures that are very painful, e.g., fracture reduction, control of the pain will be paramount. For procedures that require the child to be motionless, e.g., computerized tomography (CT) or magnetic resonance imaging (MRI) scans, immobility may be most important. Most procedures in children require some combination of analgesia and immobility along with anxiolysis, therefore sedation planning can be broadly organized into categories of these parameters.

Analgesia, hypnosis, anxiolysis or amnesia? Balanced sedation: Medication selection and dose can be organized by anticipation of whether the procedure is: (1) nonpainful/noninvasive, or associated with (2) low level of pain and high anxiety or (3) high level of pain, high anxiety, or both, (4) whether local anesthesia can be used, and (5) whether the patient needs to be motionless, i.e., for some procedures, some motion is acceptable during painful and/or invasive procedures to the extent that the motion neither causes risk to the patient nor hinders the successful performance of the procedure, whereas in others, e.g., MRI, any movement prevents completing the procedure (see Table 15.3) [61, 94, 95].

Principle and secondary effects of sedative/analgesic medications are summarized in Table 15.4. Although combining sedative/analgesic medications generally increases the risks of adverse effects [96, 97], the actual depth of sedation is likely to be a better predictor of these risks [94, 98]. Thoughtful "balanced sedation" with anxiolytic and analgesic drugs, carefully titrated to effect, can achieve very satisfactory sedation and typically results in smaller effective doses of individual drugs than if a single drug is used. For example, fentanyl is a potent analgesic but has little or no anxiolytic or amnestic effect, whereas midazolam is a potent anxiolytic and amnestic agent with no analgesic effect. Combining fentanyl and midazolam results in effective procedural sedation but the combination causes significantly greater respiratory depression than either fentanyl or midazolam alone [96].

Table 15.3 Indications and strategies for procedural sedation and analgesia [94, 95]

Pain	Anxiety	Motion	Clinical examples	Suggestion sedation strategies
No	Moderate	Some acceptable	Echo, EEG, Infant PFTs (sedation rarely needed)	Comforting, distraction Chloral hydrate PO (in patients <2 year of age) Midazolam PO
		Motionless	Computed tomography Magnetic resonance	Chloral hydrate PO (in patients <6 months of age) Pentobarbital ± Midazolam IV Propofol IV
Low or local anesthesia can be used	Moderate to high	Relatively motionless but some acceptable	Abscess incision and drainage Dental procedures, lumbar puncture Flexible fiberoptic laryngoscopy Ocular irrigation Foreign-body removal Phlebotomy, IV cannulation Laceration repair, simple Fracture reduction with hematoma block Paraphimosis reduction Sexual-assault examination	Topical or local anesthesia Comforting, distraction Oxycodone PO Nitrous oxide Midazolam PO, PR, IN, IV
High	Moderate to high	Relatively motionless but some acceptable	Abscess incision and drainage Arthrocentesis Bone marrow aspiration Burn débridement Cardioversion Foreign-body removal Complicated Fracture or dislocation reduction Hernia reduction Laceration repair, complex Paracentesis Thoracentesis Thoracostomy-tube placement	Midazolam and Fentanyl IV Ketamine IM or IV Nitrous oxide and oxycodone PO Propofol and ketamine or fentanyl IV

Table 15.4 Procedural sedation medication effects

Medication	Sedation	Analgesia	Amnesia	Anxiolysis	Emetogenic
Barbiturates	+++	–	–	–	
Benzodiazepines	+++	–	+++	+++	Antiemetogenic
Fentanyl	+	+++	–		++
Ketamine	+++	+++	++		+
Propofol	+++	–	+	+	Antiemetogenic
Chloral hydrate	++	–	–		
Nitrous oxide	++	++	+++	+++	++

Depth of sedation: Since increasing depth of sedation is associated with increasing frequency of adverse events [94, 99], use of the lightest effective sedation is usually preferred. However, frequently the depth of sedation required for a particular procedure cannot be accurately predicted in a specific patient [94]. Incompletely appreciated anxiety and lack of comprehension in younger children or those with developmental delay often cause need for deeper than anticipated sedation for procedures in which local anesthesia or mild sedation would suffice in a self-controlled adolescent or adult. For intensely painful procedures, deep sedation is typically required. Clinicians providing sedation, therefore, ideally should be trained and prepared to administer increasingly deeper sedation as guided by the patient's response to the procedure. It is important, too, for the clinician to realize that many sedative analgesic agents also induce varying degrees of amnesia. When midazolam, ketamine, or propofol, and to a lesser extent nitrous oxide, are administered, the patient is unlikely to recall clearly procedure-related pain despite occasional moaning or crying out during intensely painful parts of the procedure [9]. However, it is unwise to promise complete amnesia during the informed consent process. The extent of procedural amnesia can be assessed in part by asking the patient if he/she "recalls anything hurting" after they have recovered; a negative answer is reassuring to parents who have remained with the patient during the procedure. Because of amnesia for procedure-related pain, lighter and presumably safer levels of sedation may be acceptable when patient motion does not interfere with accomplishment of the procedure. For this reason, the amnestic agent midazolam is combined with fentanyl for PSA because completely effective analgesia cannot be achieved with fentanyl without marked respiratory depression. Of note, deeper sedation with ketamine is usually much less associated with adverse cardiopulmonary effects in comparison to other agents and, in addition, ketamine induces moderate amnesia.

Some older children may prefer not to be deeply sedated, in the same way many adults fear general anesthesia. As an example, a 13-year-old boy sedated by the author with nitrous oxide in conjunction with a lidocaine fracture hematoma block, recalled the next day the details of the reduction of his displaced distal radius and ulnar fractures. Yet, he was adamant that he would not have preferred to have been "put to sleep" and unaware of the reduction. Since the hematoma block was very effective and he recalled no pain, he was very satisfied with his experience of altered awareness during the fracture reduction. When local anesthesia or other analgesic technique can be achieved, some children may prefer lighter levels of sedation without loss of awareness, a concept that needs further investigation.

(b) Staffing

For moderate sedation, a sedation provider trained in the sedation protocol and skilled in pediatric advanced life-support techniques is responsible for the procedural sedation-analgesia, including monitoring of the patient's status. In the ED, this is typically the emergency physician. If, after induction of adequate sedation, that individual then performs the procedure for which sedation is provided, a second individual,

typically a registered nurse, with sedation training and knowledgeable in pediatric basic life-support must be at the bedside and responsible for monitoring the patient's cardiopulmonary status and the need for interventions to manage adverse events. This second individual often is responsible for recording the patient's status on the Sedation Record and may assist with minor, interruptible tasks once the patient's level of sedation and cardiopulmonary functions have stabilized, provided that adequate monitoring of the patient is maintained [59, 67, 69, 100].

For deep sedation in the ED, a sedation provider, again, typically the emergency physician, with training in the pharmacology of the agents to be administered and skilled in pediatric advanced life-support must be in the procedure room and is responsible for the procedural sedation-analgesia, including monitoring of the patient's status. At least one clinician must be assigned to monitor and record the patient's airway patency and cardiorespiratory status and, in contrast to moderate sedation planning, should have no other responsibilities during induction of sedation, the procedure and the early postprocedure period when the patient is at greatest risk for respiratory depression, partial upper airway obstruction, and aspiration. If an experienced sedation provider has induced adequate sedation and will then perform the procedure, primary responsibility for monitoring the patient's cardiopulmonary status may be designated to a second sedation trained clinician, typically a registered nurse, if the responsible provider can easily interrupt performance of the procedure to assist with or assume management of adverse events. It should not be planned that the clinician monitoring the patient would assist with the procedure as that may distract this clinician from monitoring the patient's vital signs and clinical status or interfere with rapid intervention [59, 67, 69, 100, 101]. Brief, interruptible assistance with the procedure may be provided by this person but with caution and with assured concurrent attention to the patient's vital functions. Safe use of deep sedation is dependent upon this clinician's meticulous attention to the patient's airway and breathing and anticipation and early recognition of adverse events. Threats to ventilation and oxygenation usually are easily managed when rapidly recognized and interventions immediately implemented. Experience with deep sedation has shown that some patients (~5–25%) will develop oxygen desaturation of <90% and partial upper airway obstruction, both of which are usually easily managed when rapidly recognized.

Since deeper than intended sedation may occur or be necessary in any patient, it is recommended that all but the lightest sedations, e.g., use of nitrous oxide, be staffed and monitored as if deep sedation may occur, particularly when gaining initial experience with sedation protocols or using agents with narrow therapeutic indices, e.g., propofol, midazolam + fentanyl, or etomidate. This usually means a third provider is needed if assistance will be necessary in performing the procedure. In addition, at least one provider should be present who is intimately familiar with location of resuscitation and other necessary medical equipment.

In most hospitals, physician sedation providers and nurses must be credentialed to administer PSA. Credentialing typically includes didactic sessions on use of specific PSA medications, demonstration of safe and effective administration of PSA, and competency in skills needed for rescue from adverse events [93].

(c) Monitoring and equipment

Direct patient observation: In addition to electrophysiological monitoring, airway patency, rate and depth of respiration, and the child's color (nail-beds, mucosa) should be checked frequently by vigilant direct observation, especially after each medication administration and in the early postprocedure period when painful procedural stimuli

have ended. This enables essential immediate interventions for adverse events such as marked respiratory depression, positional obstruction of the upper airway as muscle relaxation occurs (snoring, paradoxical chest wall motion without exhaled breaths may be noted), or vomiting. Opening of the airway by realignment or jaw thrust, applying painful stimulation to awaken and induce breathing, administering supplemental oxygen, or turning and suctioning to clear vomit often are usually all that is needed to correct problems that can otherwise rapidly deteriorate to life-threatening situations.

Direct monitoring during recovery should continue by a designated healthcare provider until the patient emerges to a level of moderate sedation; thereafter direct monitoring can be designated to the child's parent or another responsible adult with the healthcare provider immediately available until the patient returns to the pre-sedation level of responsiveness [59, 67, 100, 101].

Patients undergoing sedation should wear a loose fitting top or hospital gown to ensure easy direct observation of the chest. The patient's mouth and nose should not be obscured and skin should be visible for monitoring of color. A stethoscope should be immediately available.

For *moderate sedation*, in addition to direct observation, measurement of oxygen saturation by pulse oximetry is strongly recommended [59, 67, 100, 101]. Additional continuous electrophysiological monitoring throughout sedation and recovery of ECG-based heart rates, respiratory rates, and noninvasive automated blood pressures measured after each medication bolus and/or every 5 min add further measures of safety.

For *deep sedation*, in addition to direct observation, routine use of noninvasive physiologic monitoring should include continuously measured oxygen saturation, heart rate, and respiratory rate, and, in addition, noninvasive automated blood pressure measurements after each medication bolus and/or every 5 min throughout sedation and recovery [59, 67, 100, 101].

Pulse oximetry has been demonstrated to detect hypoxemia well before cyanosis occurs and is therefore critical for monitoring for respiratory compromise. In one study of infants, O_2 saturations were ≤83% before perioral cyanosis was detected by experienced emergency pediatricians [102]. Monitoring of oxygen saturation with pulse oximetry has been suggested as the most important means of reducing sedation related injury and should be used for all but minimal sedations [59, 67, 69, 98, 100, 101]. The *pulse oximeter audible tone should be activated* to alert providers to changes without the need to frequently read the monitor instead of observing the patient.

End-tidal CO_2 capnography provides breath-to-breath information on the effectiveness of ventilation and is increasingly being investigated in patients undergoing ED PSA. Assessment of ventilation by continuous end-tidal CO_2 capnography has been found more sensitive than either direct observation or decreases in oxygen saturation in detecting respiratory depression or airway obstruction. Changes in capnographic wave form and/or changes in end-tidal CO_2 are frequently noted well before changes in oxygen saturation, including in patients breathing room air [103–109]. Of note, no changes in end-tidal CO_2 were found in children sedated with ketamine alone [110, 111]. Changes in end-tidal CO_2 capnography can aid in early recognition of respiratory depression and/or airway obstruction and allow initial interventions that may avert the need to administer positive-pressure ventilations, e.g., limitation of further administration of sedative medications or opening of the airway. Assisted ventilation during oxygen desaturation due to apnea or periods of respiratory depression should be administered as needed. However, positive-pressure ventilation increases gastric pressures due to insufflation of air into the stomach. At a depth of sedation that induces apnea or significant respiratory depression, there is likely concurrent relaxation of esophageal muscle tone and significant blunting of protective airway reflexes. Thus, there is likely increased risk of pulmonary aspiration associated with positive-pressure ventilation due to gastroesophageal reflux into the oropharynx.

Routine administration of supplemental oxygen has been recommended to prevent hypoxemia during deep and moderate sedation [101]. However, sedation providers should recognize that administration of supplemental oxygen may

delay oxygen desaturation for several minutes during respiratory depression or apnea [112]. Therefore, use of supplemental oxygen may delay recognition of these adverse events with their likely concurrent depression of protective airway reflexes, unless the patient is also monitored by end-tidal CO_2 with capnography [113]. Similarly, recognition of airway obstruction is likely delayed [103–106, 108, 110, 114]. When capnography is unavailable, consideration should be given to monitoring patients by pulse oximetry as they breathe room air. Although an indirect and less sensitive measure of ventilation than capnography, decreases in oxygen saturation alert the clinician to decreases in ventilation and facilitate interventions before hypoxemia and a need for positive-pressure ventilation occurs. With this strategy, administration of supplemental oxygen may be reserved for patients whose oxygen saturations drop below 90% without rapid rise in response to airway maneuvers such as head tilt/jaw thrust and/or stimulation. Respiratory depression is sufficiently commonplace during sedation with propofol that many providers recommend as routine administration of supplemental oxygen during propofol PSA [105, 106, 115].

Equipment

Resuscitation equipment must be immediately available. A self-inflating (Ambu-type) bag-mask positive-pressure device with a PEEP attachment and appropriately sized mask, continuous oxygen supply, and an airway suctioning device with a large rigid suction tip should be prepared for each sedation. Anesthesia style CPAP bags, endotracheal intubation equipment, and resuscitation medications, with a dosing guide, including reversal agents such as naloxone and flumazenil, a paralytic agent such as succinylcholine, and antiepileptic and antiarrhythmic medications for drug induced seizures and dysrhythmias should be immediately available for all sedations [59, 67, 69, 100, 101].

No suction apparatus can clear the oropharynx during active vomiting. The patient must be helped to turn or roll to the side or to sit upright to clear his airway. The suction device is used to clear residual emesis from the mouth after active vomiting has stopped. If the patient is unresponsive and emesis is noticed in the posterior pharynx or mouth, the patient should be rapidly rolled to the side to allow emesis to passively flow out as suctioning of the posterior pharynx is performed; there is significant risk for pulmonary aspiration in this situation.

Intravenous access adds an additional invasive procedure to the patient's treatment, but it enables easily controlled and rapid titration of medications and provides an increased margin of safety by enabling rapid administration of reversal and resuscitation agents, if needed. When medications are administered intravenously, the intravenous access should be maintained throughout sedation and recovery. When medications are administered by a non-intravenous route, e.g., by intramuscular injection, whether to establish intravenous access should be decided on an individual basis. If vascular access is not established, the ability to immediately accomplish such must exist for all sedations, especially when a multiple drug sedation regimen is used. For agents that frequently cause hypotension, e.g., propofol, it is recommended that intravenous access be established with an indwelling catheter and maintained with a resuscitation fluid (lactated Ringer's solution or normal saline). Patients who have been NPO for an extended period may benefit from an infusion of 10–20 mL/kg of LR or NS to counter any hypotensive effects of sedation medications. A stopcock near the hub of the IV catheter, e.g., on the tail of a T-connector inserted into the hub of the catheter and in-line with the IV fluids, facilitates controlled and complete administration of sedation medications. This setup allows a syringe containing the sedative to be connected to the stopcock and the medication injected near the hub as the IV fluids infuse. This reduces the possibility of uncertain medication infusion amount and rate that might occur if the medication is added considerably upstream of the catheter hub. For agents such as ketamine that do not frequently cause hypotension, an indwelling "saline lock" is typically sufficient; the ketamine can be flushed into the bloodstream with 5–10 mL boluses of saline following ketamine administration.

A mnemonic some find helpful to summarize equipment preparation is MS-MAID: Machine Suction – Monitors Airway (oral airway, bag-mask, ETT, blade) IV Drugs.

Preparation for and Management of Adverse Events

Anticipation

The rarity of serious adverse events in ED PSA can lull the provider into complacency [116, 117]. It is suggested the possibility of a life-threatening event during PSA should be thought of as inevitable, as a matter of "when" rather than "if." Since these events are so infrequent and variations in individuals' responses to a medication are not always predictable, the provider must always be prepared.

Effective management of adverse events begins first and foremost with preparation for the planned sedation. Thorough pre-sedation evaluation to identify patients at increased risk for adverse events or difficult airway management, monitoring and staffing based upon intended sedation depth, and immediate availability of resuscitation equipment and medications are critical. Factors associated with serious adverse outcomes include late recognition of hypoxemia and inadequate resuscitation, thus emphasizing the importance of preparation and continual monitoring during the sedation and recovery periods [98]. If recognized early, most adverse effects can be addressed effectively with relatively minor interventions. Stimulation, airway realignment, jaw thrust, and supplemental oxygen are usually all that is needed to avoid further deterioration to life-threatening events [117].

Management of Respiratory Depression and Apnea

Respiratory depression is one of the most common potentially serious effects of pediatric PSA [66, 116, 117]. A critical incident analysis of serious adverse outcomes in pediatric sedation found 80% initially presented with respiratory depression [98]. Widespread use of pulse oximetry has since dramatically improved early recognition of respiratory depression. Agents commonly associated with respiratory depression include the sedative-hypnotics (barbiturates, benzodiazepines, chloral hydrate, propofol), particularly when used in conjunction with opioids [99, 118]. Apnea has also been rarely reported with administration of ketamine [119–121].

Avoiding respiratory depression: (see also basic pharmacokinetics) Most sedative medications variably blunt brainstem receptor response to increases in plasma levels of CO_2. Since response to rising levels of CO_2 determines breathing rate and depth, significant increases in sedative concentrations in the brainstem quickly lead to respiratory depression or apnea. The more rapidly a sedative drug is infused, the higher its initial brainstem concentration and the greater the respiratory depression. A primary strategy for reducing respiratory depression and maintaining adequate ventilation (and, in association, oxygenation) is slow administration of PSA drugs, often achieved by repeatedly infusing half or less of the total expected dose until the desired effect is achieved (titration). Ketamine can be an exception to the recommended slow administration approach because of its unique relative lack of respiratory depression. Taking advantage of first-pass kinetics, experienced sedators may choose to administer smaller doses rapidly for very brief procedures (see Section "Ketamine").

At risk periods: Patients may experience respiratory depression at any time during the sedation, but the greatest risks are immediately after medication administration and again after cessation of painful procedural stimuli [122].

Recognition of ineffective ventilation: As detailed previously, direction observation of the patient including general color and chest wall movement continues to be one of the most important means of recognizing respiratory depression and/or airway obstruction. The patient's oropharynx and chest wall should be directly visible at all times to facilitate observation for lack of respiratory effort, or respiratory effort without air exchange. In addition, *pulse oximetry with audible tone*, and *end-tidal capnography* facilitate detection of ventilatory changes before they are clinically apparent.

Airway and Ventilation Maintenance

Initial management of hypoventilation may simply require *verbal encouragement* to the patient *to breathe* as their sensitivity to rising CO_2 has been blunted by the sedation medications. Patients who have received opioids such as fentanyl may be awake but "forget" to breathe. *Stimulation*, painful

if necessary, to arouse the patient may improve muscle tone and prompt breathing. If oxygen saturations are falling despite these maneuvers, supplemental oxygen administration and airway opening maneuvers and/or positive-pressure ventilation may be necessary. See section below for management of upper airway obstruction.

Treatment: Respiratory Depression and Apnea

When monitors alarm, e.g., indicating dropping oxygen saturation, ASSESS THE PATIENT. DO NOT presume the pulse oximeter probe has slipped off, monitor malfunction, etc. Evaluate equipment later!

First Line: (in Rapid Succession, If Needed)

1. Verbally encourage or stimulate patient to breathe deeply (patients may require intensely painful stimuli, e.g., squeezing the fracture site or a hard sternal rub with knuckles); if insufficient then
2. Support airway (chin lift/jaw thrust); if insufficient then
3. Administer supplemental oxygen
4. If spontaneous ventilation continues to be inadequate, administer positive-pressure ventilation via bag/mask
5. If patient is on a continuous infusion (e.g., propofol) – slow down or stop medication infusion, then
6. Call for help, if needed

Second Line: Reversal Medications for Opioids and Benzodiazepines

If respiratory depression occurs after administration of an opioid or benzodiazepine and does not readily resolve after the above supportive measures, or requires continued positive-pressure ventilation, consider use of reversal agents. *Slow, titrated reversal* is preferred if positive-pressure ventilation is effective. The desired endpoint is lessening of the respiratory depression with slightly lighter sedation. Rapid, full reversal may lead to severe pain, hypertension, and agitation or seizure [123]. Reversal agents are rarely needed by experienced sedation providers.

Naloxone (Narcan®)

Indications: Opioid-induced apnea, respiratory depression, or "wooden/rigid chest syndrome" not responding to stimulation, airway opening maneuvers, supplemental oxygen, and/or positive-pressure ventilations.

Dose: 1–2 μg/kg (0.001–0.002 mg/kg) *IV push* repeated every 1–3 min until the patient begins to have spontaneous respirations. Doses of 1–2 μg/kg are recommended to "gently" reverse opioid-induced respiratory depression yet maintain analgesia. Larger doses, such as 10–100 μg/kg may awaken the patient and reverse the analgesic effects resulting in significant pain, hypertension, pulmonary edema, vomiting, or seizures [123].

During the interval of apnea, the patient is supported with assisted ventilations until adequate spontaneous respirations are restored. Thereafter, the patient is observed closely as the reversal effects of naloxone may be briefer than the opioid-induced respiratory depression. For "wooden chest syndrome," if the patient cannot be ventilated and oxygen saturations are dropping rapidly, naloxone may be given in 1 or 2 mg boluses for convenience. Alternatively, succinylcholine 1–2 mg/kg may be used to paralyze the patient.

Caution: opioid-induced respiratory effects may outlast the duration of naloxone and patients must be closely monitored for recurrence of respiratory depression, typically at least 2 h after naloxone administration [124].

Flumazenil (Romazicon®)

Indications: Benzodiazepine (e.g., Midazolam) induced apnea or respiratory depression not responding to stimulation, airway opening maneuvers, supplemental oxygen, and/or positive-pressure ventilation.

Dose: 0.01–0.04 mg/kg (maximum 0.5 mg) IV over 30 s. Repeat every 60 s to desired response. A cumulative dose of 3 mg may be necessary. Flumazenil may reverse midazolam-induced hypnotic and amnesic effects but may not reverse ventilatory depression [125]. When appropriate, naloxone should be used as the first line in reversal therapy. Drug therapy does not obviate the need to protect the airway and support ventilation.

Table 15.5 Naloxone & Flumazenil for reversal of respiratory depression [127]

Agent	Route	Dose	Frequency	Maximum dose (mg)	Onset	Duration (min)
Naloxone	IV, IM, or SC	1–2 μg/kg for respiratory depression 100 μg/kg (0.1 mg/kg) if unable to ventilate or *wooden chest*	Q 2–3 min as needed	2	1–2 min (IV) 15 min (IM/SC)	30–60
Flumazenil	IV	10 μg/kg (0.01 mg/kg)	Q 1 min as needed	1[a]	1–2 min, maximum effect 6–10 min	20–60

[a]If resedation after response to Flumazenil, additional doses of up to 1 mg/dose may be given q 20 min to a maximum total dose of 3 mg

Caution: Flumazenil may cause seizures in patients chronically on benzodiazepine medications and should be used cautiously in patients on medications that can lower seizure threshold. Also, benzodiazepine induced respiratory effects may outlast the duration of flumazenil and patients must be closely monitored for recurrence of respiratory depression, typically at least 2 h after flumazenil administration [126, 127]. Recurrence of sedation has been reported in up to 7% of cases, most commonly in children under 5 years of age [126] (Table 15.5).

Upper Airway Obstruction

The pediatric airway is particularly prone to dynamic obstruction due to the relatively large size of the tongue and tonsillar tissues. As sedation depth increases, the muscles of the tongue, jaw, and oropharynx loose tone in a manner similar to deep sleep. Sedation-induced "obstructive sleep apnea" may result in partial or complete airway obstruction, exacerbated by the supine position and nasal passage obstruction. A history of snoring or obstructive sleep apnea alerts the clinician to the increased likelihood of this occurrence. Placement of a shoulder roll in infants and a head roll in older children and adolescents to align the oropharynx, posterior pharynx, and trachea may help align the patient's airway and relieve this obstruction. Markedly, obese patients also may benefit from a large head or shoulder roll to compensate for their large trunk.

A jaw thrust or chin lift may be necessary to open the upper airway by pulling the tongue and related muscles away from the posterior pharynx. Patients who are very deeply sedated or have inadvertently reached the depth of general anesthesia may benefit from placement of an oro- or nasopharyngeal airway but because oropharyngeal airways may induce a gag reflex and vomiting, these devices should be used with caution. Laryngospasm is a special type of upper airway obstruction and is addressed below.

At risk periods: Positional airway obstruction may occur at any time during sedation but, in association with respiratory depression, it may more likely be shortly after medication administration or after the painful procedural stimulus has ended. Ketamine-related laryngospasm may occur in settings of current URI, unsuctioned secretions/vomitus, or stimulation of the hyperactive gag reflex during a procedure.

Recognition of upper airway obstruction: Signs of partial upper airway obstruction include stridor or noisy breathing. Paradoxical chest wall movement (sucking in of the chest and distention of the abdomen with inspiration) may be seen with partial or complete obstruction. Hypoxemia is a late sign. An obstructive pattern is seen on capnography well before changes in oxygen saturation and allows early detection of airway obstruction (or apnea).

Treatment

1. Align airway and open with chin lift or jaw thrust; provide supplemental oxygen as needed.
2. Suction airway if excessive secretions are present.

3. If not responding to repositioning, consider continuous positive airway pressure (CPAP) with bag/mask (CPAP or anesthesia type bag is preferable to self inflating-type bag as CPAP can be delivered more effectively to open the airway by distending the posterior pharynx).
4. If having difficulty maintaining an open airway, consider an oral airway (unconscious patient), or nasal airway.
5. If unable to ventilate with CPAP, rapidly consider treatment for laryngospasm with *succinylcholine*.

Laryngospasm

Laryngospasm is an uncommon but *potentially life-threatening* sedation related adverse event. It is a partial or complete upper airway obstruction, with oxygen desaturation, caused by involuntary and sustained closure of the vocal cords and is not relieved by routine airway repositioning maneuvers, suctioning, or insertion of a nasal or oral airway. Laryngospasm may be intermittent or sustained, brief or prolonged [132, 133].

The incidence of laryngospasm during pediatric ED PSA is difficult to determine as it is a rare event and large sedation databases are not available for estimation. Relative preservation of upper airway protective reflexes during ketamine-based sedation reduces the risk of pulmonary aspiration and thus makes ketamine one of the safest agents for ED PSA in unfasted children, yet, paradoxically, ketamine PSA may have increased risk for laryngospasm [134–136]. A meta-analysis of pediatric ketamine-based ED PSA found an incidence of laryngospasm of 0.3%; the only identifiable association with increased risk of laryngospasm was an initial intravenous dose of greater than 2.5 mg/kg but data was unable to be analyzed for associations with URI, wheezing, or other risk factors found to be associated with increased risk during general anesthesia [137]. Of particular interest, young age and oropharyngeal procedures (excluding endoscopy) were not associated with increased risk but prospective larger data sets are needed to better clarify these risks.

Laryngospasm in almost 50,000 non-intubated children undergoing elective propofol sedation/anesthesia was noted to occur at a rate of 21/10,000 (0.2%) [86]. Laryngospasm associated with general anesthesia has been estimated as high as 14% in younger children and as low as 0.1%, with lower likelihood reported in non-intubated children [138, 139]. The wide variability may be due to differences in definition and study design, patient populations, anesthetic techniques, and airway manipulation [140]. However, consistently noted risk factors for laryngospasm include young age, upper respiratory infection, asthma, manipulation of the airway, and exposure to smoking in the home [141, 142].

It is unclear whether prophylactic administration of atropine or glycopyrrolate with ketamine to reduce hypersalivation reduces the risk of laryngospasm [143, 144]. The meta-analysis of pediatric ketamine-based ED PSA, noted earlier, found that overall airway and respiratory adverse events (but not laryngospasm) were actually increased in children who received concurrent anticholinergics; [137] this unexpected association needs further investigation.

At risk periods: Laryngospasm may occur at any time during sedation, including recovery. In one report of non-intubated children undergoing sedation/general anesthesia, laryngospasm occurred most frequently during emergence (48%), but was also seen during induction (29%) and maintenance (24%) phases [139]. Increased risk for ketamine-related laryngospasm may occur in children with current URI, especially if febrile, if secretions/emesis pool in the posterior pharynx, or if a procedure such as endoscopy stimulates the gag reflex [142, 145, 146].

Recognition of laryngospasm: Early signs of laryngospasm may include coughing. A characteristic stridulous noise can be heard with partial laryngospasm. Chest wall movement is noted but there is a mismatch between the patients' respiratory effort and the small amount of air exchange. If complete laryngospasm occurs, no stridulous noise will be heard and no air exchange or breath sounds will be

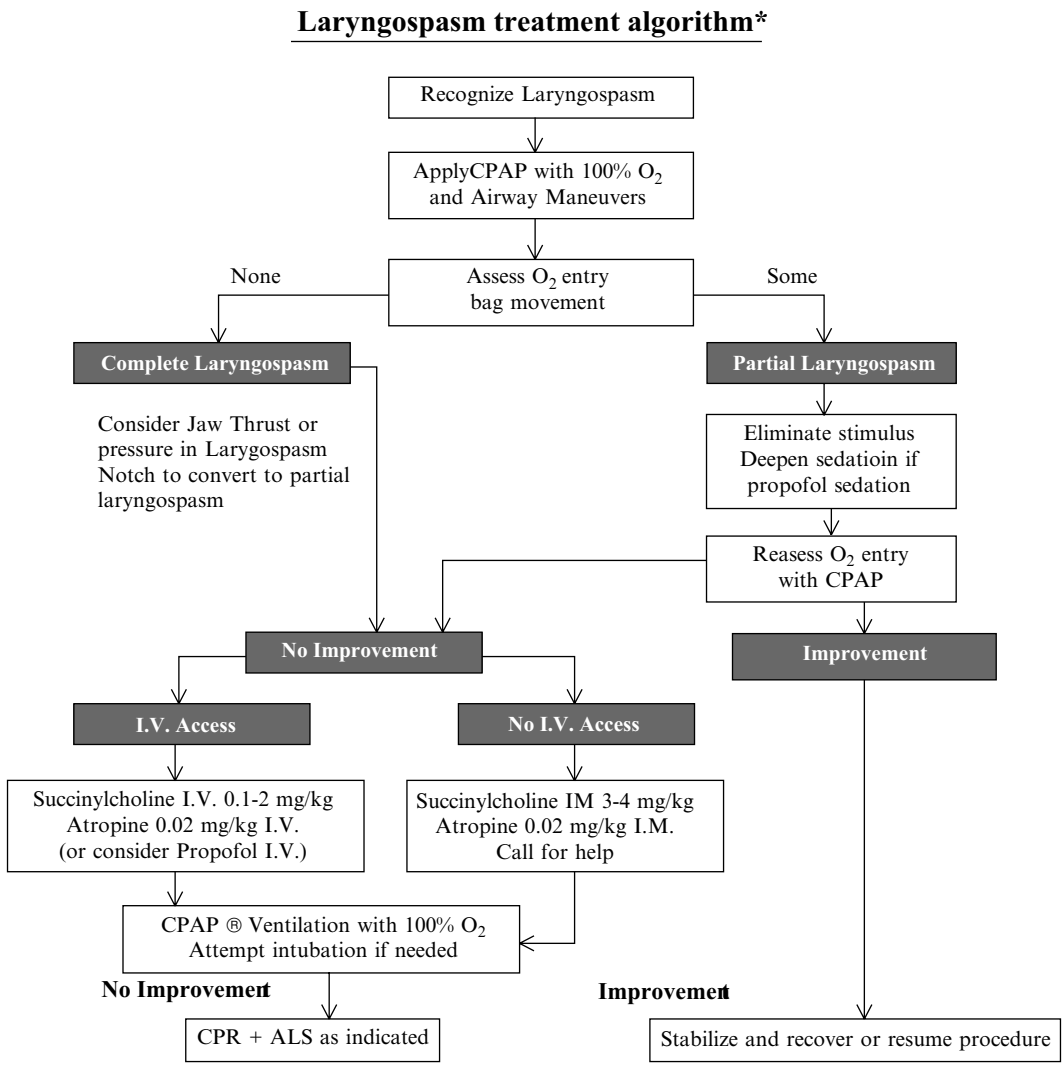

Fig. 15.2 Laryngospasm treatment algorithm (Modified for sedation from Hompson-Evans et al. [361])

noted despite chest wall movement. No ventilation with a bag-mask device will be possible.

Oxygen saturations will drop rapidly if the patient is breathing room air, typically within 30–60 s. If the patient has been preoxygenated, saturations may remain above 90% for 1–5+ min, dropping more rapidly in younger children and infants [112]. Capnographic changes are a very sensitive means of diagnosing laryngospasm. During partial laryngospasm, turbulence affects expiratory flow but the amplitude of the capnogram will correlate with the extent of hypoventilation. During complete laryngospasm the CO_2 waveform will be lost despite chest wall movement [108].

Treatment: (Fig. 15.2) [136] If the patient develops stridor during sedation:

1. *Remove stimulus* to posterior oropharynx; consider gentle suction of excessive secretions, emesis.

2. *Reposition airway* with jaw thrust; vigorous, painful intrusion of the thumbs in the *laryngospasm notch*[2] may help.
3. *Apply CPAP* (continuous positive airway pressure) *with 100% O_2* with anesthesia type bag/mask; CPAP may reduce partial obstruction by distending the posterior pharynx which exerts pull to open the partially closed larynx and vocal cords.
4. *Assess air movement*; if unable to oxygenate with CPAP.
5. Rapidly consider *Atropine 0.02 mg/kg I.V. followed by low-dose succinylcholine* (*0.1–0.25 mg/kg I.V.*) with ventilatory support as needed; [147] consider an additional dose of *propofol* if propofol sedation is underway.
6. If still unable to oxygenate, administer *full-dose succinylcholine* (*1–2 mg/kg I.V. or 3–4 mg/kg I.M.*) followed by intubation.

Attempts to provide intermittent positive-pressure ventilation with a face-mask may distend the stomach and make subsequent ventilation more difficult. In complete laryngospasm CPAP may worsen the obstruction by forcing the area just above the false cords closed. Therefore if complete spasm cannot be broken, early IV agents should be considered [136].

When laryngospasm occurs in the midst of propofol PSA, deepening the sedation with administration of an additional 0.5 mg/kg of propofol has been shown to be an effective treatment for laryngospasm [148]. Transient apnea with this technique should be anticipated.

Low-dose succinylcholine (0.1 mg/kg IV) may be effective in relaxing laryngospasm [147]. Onset of neuromuscular blockade is generally more rapid at the larynx compared with the peripheral muscles [149]. Relaxation of the larynx induced with this small dose will be brief but may allow the patient to be oxygenated by CPAP and intubation avoided. Alternatively, administration of a fully paralyzing dose (1–3 mg/kg IV) followed by intubation should be considered if the patient is rapidly becoming severely hypoxic [136]. The intravenous route is preferred for administration of succinylcholine, but if there is no vascular access, it can be administered intramuscularly at a dose of 3–4 mg/kg. Although full effect may take about 4 min, onset of relaxation of the larynx occurs earlier than maximum suppression of the muscle twitch response and enables ventilation [150].

Succinylcholine administration following hypoxia may be associated with severe bradycardia and even cardiac arrest. *Atropine 0.02 mg/kg I.V.* administered prior to succinylcholine is recommended [151].

Emesis

Nausea and vomiting occur in 5–25% of children during or after ED PSA. Use of opioids before or during sedation increases the likelihood of vomiting [88, 152], whereas concurrent use of midazolam with an opioid [9] ketamine [87], or nitrous oxide [10] reduces the incidence of PSA-related vomiting. Propofol appears to be less emetogenic and may not benefit from addition of midazolam to the regimen. Coadministration of ondansetron (Zofran®) with ketamine reduces vomiting both in the ED and after discharge [92]. Children with a history of prior postoperative nausea and vomiting or with a history of motion sickness are at increased risk for vomiting [153]. Further investigations are needed to better predict sedation associated nausea and vomiting and to determine strategies to significantly reduce this relatively minor but very undesirable adverse effect.

At risk periods: Emesis may occur at any point during procedural sedation, but most commonly is seen during the postprocedure recovery period [9, 10, 88]. Since emesis can occur at any point and with every systemic agent used for procedural sedation, the provider responsible for monitoring the patient's airway should always be vigilant for signs of impending retching and prepared to turn

[2]The laryngospasm notch is behind the lobule of each ear, between the ascending ramus of the mandible and the mastoid process and the base of the skull. Painful pressure at this point over the styloid process is thought to cause afferent input that causes relaxation of the cords by a poorly defined mechanism. This maneuver may also be a modified jaw thrust.

the patient to the side to clear the airway. Suction equipment should be prepared and immediately available during and after all sedations. This equipment is used to finish clearing the emesis from the mouth after the patient stops vomiting. It is also advisable to have a large emesis basin at the bedside during each ED PSA.

Treatment: Emesis During Procedural Sedation

- Position patient's head to side, allow patient to clear own mouth during active vomiting, suction oropharynx with rigid large bore Yankaur type suction tip.
- If using nitrous oxide, immediately remove the mask to allow clearing of emesis and discontinue nitrous use, at least temporarily. It is preferred to allow the patient to hold the facemask during sedation with nitrous oxide so that they can immediately remove the mask if they feel nauseated.

Ondansetron (Zofran®)
An anti-serotonin agent, is not routinely administered to prevent emesis during ED PSA. However, one study of children receiving ketamine for ED PSA, vomiting in the ED or after discharge was less frequent with ondansetron coadministration: (8 vs. 19%), with 9 patients needing to be treated to prevent one episode of vomiting [92]. Ondansetron also may be considered in a child with significant prior history of postoperative nausea and vomiting. Further evaluation of the effectiveness of this antiemetic agent during ED PSA is needed. Other antiemetic agents such as prochlorperazine (Compazine®) or promethazine (Phenergan®) usually are not used because of sedating effects and increased risk for causing dystonic reactions.

Dose: IV, PO: 0.1–0.15 mg/kg, maximum dose 4 mg. Rapidly-dissolving 4 mg oral tabs (ODT) are available and can be split in half for easy administration to young children. Dosing can be simplified by administering ondansetron ODT 2 mg to children 3 years of age and younger and 4 mg to children 4 years of age and older.

Cautions: May rarely cause bronchospasm, tachycardia, headaches, and lightheadedness.

Not requiring patients to drink fluids prior to discharge also may reduce vomiting. Historically, assuring patients can drink prior to discharge has been done to prevent postoperative "dehydration." Given shortened fasting times and the common practice of administration of IV fluids during sedation, the risk of dehydration is low compared to the risk of inducing vomiting [152].

Pulmonary Aspiration

Clinically significant or life-threatening pulmonary aspiration of gastric contents during pediatric procedural sedation is extremely rare. Aspiration occurs in approximately 0.1% of cases under general anesthesia and was noted to have occurred in 4 of 49,836 children undergoing elective propofol sedation/anesthesia but it has not been reported in association with ED PSA [72, 73, 78, 86]. Patients with ASA Physical Status Class III or higher and those requiring intubation are likely at higher risk. Risk for aspiration is likely greater, too, in patients who experience brief periods of apnea or significant respiratory depression as esophageal tone and protective airway reflexes may be absent during these periods and gastric contents may reflux into the trachea with little or no initial patient response. Because of the potential gravity of this adverse event, it is suggested clinicians consider using ketamine or nitrous oxide that better preserve protective airway reflexes or, when possible, lighter sedation combined with local anesthesia for non-fasted emergency patients [154].

Recognition: Clinical symptoms of pulmonary aspiration may include cough, crackles/rales, decreased breath sounds, tachypnea, wheeze, rhonchi, or respiratory distress that were not present before the sedation and present before the end of the ED recovery phase. These are usually accompanied by a decrease in oxygen saturation from baseline, requiring supplemental oxygen, and, if obtained, focal infiltrate, consolidation or atelectasis on chest radiograph [78, 132]. As noted previously, clinically significant pulmonary aspiration may more likely occur in the unresponsive

patient when gastric contents passively flow out of the stomach to the larynx. As the aspiration occurs, there may be little or no immediate signs due to the depth of sedation/anesthesia. The aspiration may become evident as the patient emerges from sedation.

Treatment: If emesis is seen, turn patient to side, allow to retch, and suction posterior pharynx as needed. Administer supplemental oxygen by nasal cannula or mask as needed. Many cases of transient hypoxia will resolve with this simple maneuver. CPAP may improve oxygenation in cases of severe aspiration with alveolar collapse. The majority of children who experience pulmonary aspiration require only close observation and simple supportive care with supplemental oxygen with or without CPAP and recover without sequelae [72, 73, 82, 86]. Endotracheal intubation should be considered if definitive protection of the airway or tracheal suctioning is required; RSI (rapid sequence induction) may be necessary. Uncommonly, severely symptomatic patients may need to be taken to the OR for emergent bronchoscopy with bronchial lavage of particulate matter. Arrange for appropriate continued monitoring, support and work-up as needed including chest radiograph. For symptomatic patients, this usually means inpatient admission to an intensive care unit.

Medications

Basic Pharmacokinetics, Simplified

Parenteral drugs effective for PSA are small, hydrophobic lipophilic compounds that rapidly diffuse out of the bloodstream into the lipophilic tissues of the brain and spinal cord where they cause sedation/anesthesia.

Since the brain receives a disproportionately high percentage of the cardiac output (15–25%) [155], a large portion of a sedative drug injected into the bloodstream circulates on first-pass out of the heart into the brain's circulation and quickly crosses the blood–brain barrier to exert its clinical effects within a single circulation time (first-pass or "one arm-brain" kinetics). As the drug circulates throughout the body and diffuses into muscle, bone, and, at a slower rate, into poorly perfused fat, the blood plasma concentration falls. The concentration gradient between the brain and the blood then favors drug diffusion out of the brain. As the brain's drug concentration falls, the drug effect lessens. This secondary re-equilibration ("bi-phasic redistribution") causes the patient to awaken or respiratory depression to lessen. These effects are relatively independent of metabolic clearance of the drug from the body. PSA drugs' metabolic half-lives tend to be on the order of hours whereas their sedative effect half-lives or "wake-up times" are on the order of minutes [156].

The duration of action of a single intravenous dose is similar for all these anesthetic/hypnotic drugs and is determined by redistribution of the drugs out of the brain. However, after repeated doses or prolonged infusions, a drug's duration of action is determined by complex interactions between the rate of redistribution of the drug, the amount of drug accumulated in fat, and the drug's metabolic clearance. The wake-up time of some drugs such as etomidate, propofol, and ketamine increase only modestly with prolonged infusions while others such as diazepam and thiopental increase dramatically and midazolam less so [156].

A rapidly injected drug travels as a more concentrated bolus on the first-pass out of the heart into the brain circulation than a slowly injected drug that is diluted by the passing blood. Thus, with rapid infusion, the initial concentration gradient between the plasma and the brain is greater. Consequently, the brain's concentration of the drug rises more rapidly and a greater portion of the administered dose enters the brain with resultant deeper sedation than when the same drug dose is slowly infused.

Thus, small doses of medications can have significant clinical effect if administered rapidly. Since the blood–brain concentration gradient also reverses more rapidly with these smaller doses, "wake up" time may be shorter making this strategy beneficial for brief procedures. Importantly, however, clinicians must be aware that rapid changes in the brainstem's concentration of opioid and sedative drugs markedly

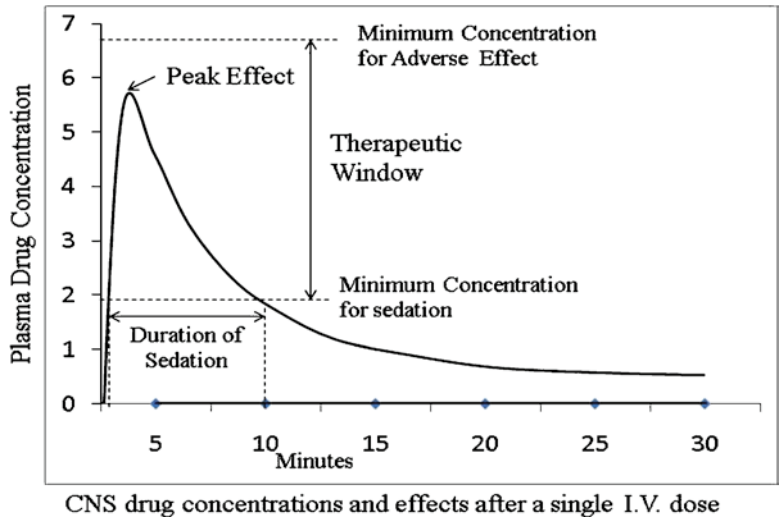

Fig. 15.3 Plasma drug concentration and CNS drug concentrations and effects after a single IV dose

increase the potential for respiratory depression and apnea. As a practical point, this technique can be used only for ketamine administration because it causes markedly less respiratory depression than opioid and GABAergic drugs. This technique needs further study to delineate its safety and effectiveness and is suggested for consideration only by clinicians with extensive experience in ED PSA (Fig. 15.3).

A drug's *Therapeutic Window* is used to describe the difference between the dose of that drug that results in the desired sedative or analgesic effect and the dose that results in adverse effects. A drug with a wide therapeutic window has a greater margin of safety for use for ED PSA. For example, accidental administration of a tenfold greater than intended dose of ketamine will likely result in prolonged recovery but relatively little cardiopulmonary depression [157], whereas the same error with propofol will result in apnea and hypotension [158].

Many reasonable medication options exist for ED PSA [76, 159]. Use of analgesic medication when pain is the primary cause of distress is the key and balancing analgesia with anxiolysis makes sedations more pleasant for patients. For nonpainful procedures when immobility is the primary objective, sedative/hypnotic medications may be chosen. It is recommended that the clinician initially become familiar with a few specific agents or combination of agents that provide the desired effects of analgesia, sedation, and/or anxiolysis. Limiting one's experience to a few agents better enables one to anticipate and manage adverse effects and events associated with those agents. One's pharmacologic armamentarium then can be gradually increased and refined with tailoring of regimens to a specific patient's characteristics. The following section summarizes medication effects and pharmacology in healthy children. Abnormalities in renal and hepatic function can significantly alter these parameters, particularly the duration of effects. In addition, significant variability in effect may occur between individuals due to genetically determined factors such as differences in drug receptor sites, metabolic activation, or clearance. Patients with ASA Physical Status III and higher also have less physiological reserves and therefore are more likely to have adverse effects with smaller doses.

Dosing Details

Titration to Desired Effect

Careful intravenous "titration" of medications using repeatedly administered small doses to achieve the

desired clinical effect enables the practitioner to use the smallest effective dose and reduce the peril of over-sedation with its increasing risks of respiratory depression and aspiration, and, furthermore, hasten recovery [69, 96, 101, 160]. Individual variation in sensitivity to the medication can also be detected, thus a smaller than expected dose may be found adequate for a given individual.

Knowledge of the time to peak effect of the specific medication is necessary to avoid "stacking" of doses when first gaining experience with titration. That is, if, to achieve deeper sedation, a subsequent dose is administered before the peak effect of the preceding dose has occurred, deeper than intended sedation can easily occur. For example, morphine has a peak effect of approximately 10 min. If an additional dose of morphine is administered after 5 min because the patient is still in significant pain, by 15 min after the original dose, when both the first and second doses are near peak effects, the patient may have significant respiratory depression due to an excessive accumulative dose. For this reason, titration is difficult with drugs that have longer than 1–3 min to peak effect time.

When a "typical" total dose for a specific procedure is known, that total dose may be divided and the increments administered at intervals shorter than "the time to peak effect" without likely overshoot. This strategy of repeated administration of fractional doses for fixed dose protocols, e.g., half of the anticipated total dose administered twice with administration separated by a short interval, reduces the risk for significant respiratory depression induced by some agents such as the combined technique using fentanyl and midazolam. This approach is suggested for providers who have less experience with a specific medication.

Intravenous Administration at the Hub

Injecting medications at or near the hub of the indwelling venous catheter allows one to know more precisely when the drug enters circulation and when the entire dose has been administered. This can avoid unintended continued infusion of residual drug in the intravenous tubing when adverse effects are occurring.

Intramuscular Administration

While IM administration avoids the need for placement of an IV catheter, it still requires a feared needlestick and makes titration to effect difficult. More importantly, if a serious adverse event occurs, e.g., severe laryngospasm, an emergent IV for resuscitation medications or fluids may be difficult to place. Specifically, ketamine administered IM has been shown to be effective in achieving sedation. However, the IM route requires either use of a dose large enough to sedate all children, e.g., 4 mg/kg, which will over-sedate some and result in greater frequency of adverse events [137], or painful repeat administration of a smaller dose if the original dose is insufficient. Since the onset of IM ketamine is 5–15 min, titration without over-sedation is difficult. Due to the large dose typically administered IM, recovery is prolonged [161].

Sedative/Hypnotic Agents

Commonly used sedative-hypnotic medications for procedural sedation include the barbiturates, chloral hydrate, propofol, and etomidate. These drugs induce general depression of the central nervous system (CNS) by stimulation of inhibitory gamma-aminobutyric acid (GABA) receptors or other mechanisms which are not yet fully elucidated. None of these drugs have an analgesic effect. While deeply induced sedation, e.g., with propofol, may enable painful procedures to be accomplished, lighter sedation with less respiratory depression may be facilitated by the addition of an analgesic agent as described in subsequent sections. This chapter will review the common sedatives used in the ED with particular focus on their clinical applications and supporting literature from the speciality.

Chloral Hydrate [76]

Indications: Chloral hydrate may be used to provide effective ED PSA in children less than 2 years of age, including those with congenital cardiac anomalies, who are undergoing painless diagnostic studies such as CT and MRI scans. Sedation is achieved

in >80% of young children. Chloral hydrate should not be considered a first line agent in children older than 48 months because of decreased efficacy as compared with younger children. The drug may be administered orally or rectally. The oral preparation has a bitter taste that frequently requires administration in a flavored vehicle to disguise its taste; approximately a third of children may vomit soon after oral administration.

Contraindications/cautions/adverse effects: Children receiving chloral hydrate should be properly monitored and managed by appropriately trained personnel due to the risk of respiratory depression and hypoxia. Chloral hydrate should not be used in children with neurodevelopmental disorders due to an increased incidence of adverse effects and decreased efficacy as compared with healthy children. Chloral hydrate has the potential for resedation and may produce residual effects up to 24 h after administration. The elimination half-life is age dependent with much longer effects in infants. These effects may occur long after the procedure is finished; reports describe infant deaths due to slumping in car seats with obstruction of the airway after discharge. Many infants may have unsteady gait, hyperactivity, or irritability the day after sedation. Other adverse effects include respiratory depression, hypotension, paradoxical excitement (0–15%) vomiting (10–30%), and rarely, hepatic failure, areflexia, jaundice, gastrointestinal hemorrhage, and esophageal stricture [76, 162, 163]. These disadvantages along with its highly variable effects on older children and inherent difficulty with titration of oral medications make this agent less than ideal for children older than 1–2 years of age. Interestingly, children who have been fasted may have increased PSA failure rates. See Mace et al., for further details on dosing and adverse effects [76].

Pregnancy category C

Dose: PO or PR: 50–125 mg/kg; typical initial dose 75 mg/kg. A second dose may be given, if needed, to a maximum of 2 g or 100–125 mg/kg total dose.

Onset/duration: sedation within 30–60 min, recovery by 60–120 min.

Mechanism of action: halogenated hydrocarbon with sedative-hypnotic but no analgesic effects.

Metabolization: rapidly metabolized by hepatic alcohol dehydrogenase to its active compound trichloroethanol and subsequently excreted in the urine [156]. The elimination half-life is age dependent; 40 h in preterm infant, 28 h in term infant, 6–8 h in toddler.

Barbiturates

Barbiturates are pure sedatives with no analgesic effect. They potentiate the effect of gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the CNS, by binding to the $GABA_A$ receptor and prolonging the open time of the membrane chloride ion channel. In addition, barbiturates block the excitatory AMPA receptor [156].

Methohexital (Brevitol®)

Indications: Methohexital administered by either the intravenous, intramuscular, or rectal route can provide effective sedation for children undergoing painless diagnostic studies such as CT or MRI scans. However, because of the readily induced respiratory depression associated with this medication, methohexital has not been used or studied extensively for procedural sedation in children and thus its use should be considered only by experienced and knowledgeable clinicians.

Adverse effects: Respiratory depression and apnea are dose and infusion rate-dependent and are readily induced with intravenous administration but may occur with any route of administration. Hangover-like residual effects may last for 24 h.

Pregnancy category B

Dosages: 1 mg/kg IV; 10 mg/kg I.M.; 25 mg/kg P.R.

Onset/duration: IV: sedation within 30 s, recovery by 20–30 min [164]

PR: sedation within 6–9 min, recovery by 40–60 min [165, 166].

Mechanism of action: ultrashort-acting, highly lipid soluble barbiturate with rapid CNS uptake and redistribution. It has marked sedative-hypnotic but no analgesic effects.

Metabolization: Hepatic degradation with renal excretion results in an elimination half-life of 3.5 h and less accumulation of drug in body tissues compared to other barbiturates.

Pentobarbital (Nebutal®)

Indications: Pentobarbital is a short-acting barbiturate that induces relative immobility and can be safely used to sedate children to facilitate non-painful diagnostic studies such as CT and MRI scans redundant, but supportive measures may include head positioning, supplemental oxygen, and occasional bag-valve-mask ventilatory support [159]. Pentobarbital successfully sedates >97% of children for CT or MRI scans with higher success rates in children younger than 8 years of age [167–169]. Pentobarbital is more effective in providing sedation than midazolam [170] or etomidate [171] and causes fewer adverse respiratory event than propofol [172]. The addition of midazolam with pentobarbital does not appear to increase success rates and prolongs time to discharge [168].

Oral pentobarbital (4 mg/kg) has been found similar to oral chloral hydrate (50 mg/kg) in time to sedation and length of sedation; overall adverse event rate, including oxygen desaturation, was slightly lower with pentobarbital (0.5%) than with chloral hydrate (2.7%) [173, 174]. Of note, a database review found infants younger than 12 months of age sedated for elective CT or MRI with PO pentobarbital (4–8 mg/kg) had comparable effectiveness and fewer respiratory complications compared with IV pentobarbital (2–6 mg/kg); time to sedation was slightly longer with PO than with IV pentobarbital (18 vs. 7 min), but time to discharge (~1 h 45 min) was similar. Total adverse events rate was similar (0.8% [PO] vs. 1.3% [IV]), but oxygen desaturation was slightly more frequent for IV (0.2% [PO] vs. 0.9% [IV]). Sedation effectiveness was comparable (99.5% [PO] vs. 99.7% [IV]), leading the authors to recommend consideration of PO administration for this age group, even when an IV is in place [175]. In a randomized comparison of IV pentobarbital (maximum 5 mg/kg in incremental doses) or oral chloral hydrate (75 mg/kg) prior to MRI, children who received pentobarbital had a higher incidence of paradoxical reaction (14 vs. 9%) and prolonged recovery with a similar failure rate [174].

Adverse effects: Respiratory depression is dose and infusion rate-dependent and is generally less than that seen with equivalently sedating doses of opioids or chloral hydrate [173, 174, 176]. Mild respiratory depression is usually seen at doses required for hypnotic effect. The following adverse events and frequencies have been reported; transient respiratory depression with oxygen desaturation of ≥10% below the baseline in 1–8%, vomiting in ≤1% [168, 177, 178], increased airway secretions, airway obstruction, coughing, and bronchospasm [167–169, 173, 177–179], emergence reactions (hyperactivity in 5–7%) [177, 179] 8.4% in children older than 8 years [179], paradoxical reaction (sustained inconsolability and severe irritability and combativeness for more than 30 min) in 0.01% with oral pentobarbital [173], and in 1.5% with intravenous pentobarbital [168]. Up to 35% of children will have increased sleeping or hangover-like effects in the 24 h following pentobarbital sedation [173, 179]. Pentobarbital should be avoided in children with porphyria.

Pregnancy category D

Dosages: *IV*: Protocol used by author: first dose: 2.5 mg/kg; if needed, subsequent doses: 1.25 mg/kg, may repeat × 3 to maximum of 7.5 mg/kg or 200 mg maximum.

IM: 2–6 mg/kg, to a maximum of 100 mg.

PO or PR (*<4 years*): 3–6 mg/kg, to a maximum of 100 mg.

PO or PR (*>4 years*): 1.5–3 mg/kg, to a maximum of 100 mg.

Onset/duration: The onset of action is related to the route of administration and subsequent absorption. The duration of hypnotic effect is dependent upon redistribution with recovery occurring within 50–75 min after IV or IM administration, even though the biologic half-life in plasma is 15–20 h [176].

After IV administration: sedation by 1–10 min (peak by 5–10 min), recovery by 1–4 h; most patients awakening within 30–60 min [168, 170].

After IM administration: sedation by 10–30 min, recovery by 2–4 h.

After PO administration: sedation by 15–60 min, recovery by 2–4 h.

Mechanism of action: short-acting barbiturate with sedative-hypnotic but no analgesic effects; it induces relative immobility through nonselective depression of the CNS via facilitation of GABA receptors.

Metabolization: hepatic degradation with elimination half-life 15–20 h [176]. This may explain why many parents note it may take their children up to a day to return to normal behavior.

Anxiolytic-Amnestic Sedative Agents

Benzodiazepines

Benzodiazepines produce a range of hypnotic (sedative), anxiolytic, amnestic, anticonvulsant, and muscle relaxant effects via modulation of the $GABA_A$ receptor, the most common inhibitory receptor within the brain. The $GABA_A$ receptor is composed of five subunits each of which has multiple subtypes. The varying combinations of subunit subtypes result in different pharmacological and clinical effects (Table 15.6). When the benzodiazepine binds to its site on the $GABA_A$ receptor, it causes the receptor to have a much higher affinity for the GABA neurotransmitter. This results in the associated chloride ion channel opening more frequently causing the neuronal membrane to become hyperpolarized [156]. Benzodiazepines have no analgesic effect. Benzodiazepines administered without other medications rarely cause severe adverse effects [180]. However, when benzodiazepines are combined with other drugs such as opiates, marked respiratory depression and apnea can readily occur [96]. Midazolam (Versed®) and Diazepam (Valium®) are commonly used benzodiazepines for procedural sedation because of their shorter duration and potent anxiolytic and amnestic effects.

Paradoxical Reactions

Severe behavioral changes, typically during recovery, resulting from benzodiazepines as well as barbiturates have been reported including mania, anger, and impulsivity. Individuals with borderline personality disorder appear to have a greater risk of experiencing severe behavioral or psychiatric disturbances from benzodiazepines. Paradoxical rage reactions from benzodiazepines are thought to be due to partial deterioration from consciousness, generating automatic behaviors, fixation amnesia, and aggressiveness from disinhibition with a possible serotonergic mechanism playing a role [181, 182]. In the context of ED PSA, parents should be forewarned about the possibility of excitability, increased anxiety, and agitation in response to midazolam. Recommendations for management of this adverse effect include protecting patients from self-harm while allowing further recovery, deepening sedation with fentanyl or diphenhydramine or administration of caffeine [181, 183].

Midazolam (Versed®)

Indications: Midazolam is a water soluble benzodiazepine that induces anxiolysis and mild sedation. Most children will not fall asleep with midazolam alone, even at higher doses. Consider another agent or combine with another agent, e.g., pentobarbital, if procedure requires patient to remain motionless (e.g., MRI scan). Midazolam has more potent amnestic effects, quicker onset and shorter duration of action compared to

Table 15.6 Comparison of benzodiazepines

Drug	Dose (mg/kg)	Onset (min)	Peak effect (min)	Duration (h)
Midazolam	0.05–0.15	1–3	3–5	0.5–1
Diazepam	0.1–0.2	1.5–3	1–2	2–6
Lorazepam	0.03–0.05	1–5		3–4

diazepam [184–187]. Since it is water soluble, midazolam can be administered intramuscularly, as well as PO, IV, or intra-nasally (IN). Midazolam may be used for seizure control but longer-lasting agents such as lorazepam are typically used. Midazolam also has antiemetic effects, an additional benefit when coadministered with opioids or ketamine [188].

Contraindications/cautions/adverse effects: Midazolam causes minimal hemodynamic effects (mild hypotension with compensatory tachycardia) but dose and infusion rate-dependent respiratory depression and apnea occur when midazolam is administered in concert with opioids [96]. An important adverse reaction to benzodiazepines in children is the disinhibitory reaction, possibly mediated by central cholinergic mechanisms [181]. Paradoxical excitement or dysphoria during recovery may be increased in older children when midazolam is coadministered with ketamine [87].

Pregnancy category D

Dosages:

IV/IM: Anxiolysis: 0.05 mg/kg IV with maximum of 2 mg; Sedation: 0.1 mg/kg IV with maximum of 5–10 mg. If titrating to effect, administer doses at 3 min or greater intervals to avoid stacking effects. However, the anticipated dose, e.g., 0.1 mg/kg may be divided and administered at 1–2 min intervals to reduce respiratory depression.

PO: 0.2–0.75 mg/kg.

IN: 0.2–0.4 mg/kg (use 5 mg/mL IV solution to reduce volume, use atomizer, or drip slowly): more rapid onset and shorter duration than oral. When administered with an atomizer device, this technique is well tolerated and effective to achieve mild to moderate sedation [189]. If the intravenous solution is dripped into the nares without atomization most children complain of a burning sensation [190–192].

PR: 0.3–0.5 mg/kg, may not be preferred by older children [193, 194].

Onset/duration:

IV: sedation within 1 min, peak effect by 2–6 min, recovery by 30–60 min [195].

IM: sedation within 5–15 min, peaks by 30 min, recovery by 30–60 min [196].

PO: anxiolysis and mild sedation peak within 15–20 min, recovery by 60–90 min [190].

IN: effect within 5–10 min, duration 45–60 min. Use of atomizer results in faster onset.

PR: sedation within 5–10 min, recovery 60 min [193, 194].

Mechanism of action: (see benzodiazepine introduction).

Metabolization: Midazolam is degraded almost completely by cytochrome P450-3A4 in the liver and excreted in the urine. Midazolam metabolites have little CNS activity, unlike those of diazepam.

Pregnancy category D

Reversal: Midazolam-induced apnea or respiratory depression may be counteracted by administration of *flumazenil 0.01–0.04 mg/kg* (*maximum 0.5 mg*) *IV over 30 s* and repeated every 60 s to desired response. A cumulative dose of 3 mg may be necessary. Flumazenil may reverse midazolam-induced hypnotic and amnesic effects but not ventilatory depression [125]. The patient must be closely monitored, typically for 2 h after flumazenil administration, for resedation and respiratory depression. Recurrence of sedation has been reported in up to 7% of cases, most commonly in children under 5 years of age [126]. Flumazenil may cause seizures in patients chronically on benzodiazepine medications and should be used cautiously in patients on medications that can lower seizure threshold.

Diazepam (Valium®)

Indications: Diazepam has excellent antianxiety, skeletal muscle relaxation, and amnestic properties but because its duration of effect is longer than that of midazolam, diazepam is seldom used for ED PSA or preprocedure anxiolysis. It is considered 2–4 times less potent than midazolam.

Contraindications/cautions/adverse effects: Drowsiness may last 2–6 h with resedation occurring at 6–8 h due to enterohepatic recirculation and formation of active metabolites. Like other benzodiazepines, diazepam readily causes respiratory depression with rapid administration.

Diazepam's propylene glycol carrier causes burning sensations on intramuscular and intravenous injection, and erratic absorption with intramuscular administration. Administer with caution in patients with liver and kidney dysfunction.

Dosages: IV: 0.04–0.2 mg/kg/dose q 2–4 h.
PR: 0.5 mg/kg/dose.
PO: 0.12–0.8 mg/kg.

Onset/duration: IV: within 1.5–3 min.
PR: 7–15 min.
PO: 30–60 min.

Mechanism of action: (see benzodiazepine introduction)

Metabolization: Diazepam undergoes hepatic microsomal oxidation with renal excretion. Liver and kidney dysfunction, as well as active metabolites including desmethyldiazepam and oxazepam, may prolong effects.

Pregnancy category D

Other Non-Analgesic Sedative Agents

Propofol (Diprivan®)

Propofol is a sedative hypnotic agent with no analgesic properties [156]. It is the most commonly used parenteral agent for induction and maintenance of general anesthesia in the United States, due in large part to rapid and pleasant recovery from anesthesia induced by this potent agent [156]. Little or no nausea is associated with propofol and it's amnestic effect is similar to that from midazolam [197]. Many adults and older children remark on awakening that they feel as if they have just had a good nap. These characteristics have resulted in propofol's rapid increase in popularity as an agent for scheduled [86, 198] and ED PSA for children [159, 199].

Propofol, however, has a narrow therapeutic window which makes PSA titration to desired effect without over-sedation more difficult than with many other agents. Significant respiratory depression and hypotension are relatively common (see Adverse Effects section) [86, 200]. Propofol can be used alone for painless procedures such as MRI or CT scans, or, at greater doses, for painful procedures. However, because significant respiratory depression or apnea are associated with doses necessary for painful procedures, smaller doses of propofol have been combined with analgesic opiates or ketamine for ED PSA [200–202]. Although combining ketamine with propofol may have theoretical benefit by using lower doses of each agent to reduce the undesirable adverse effects of both agents, a 2007 review of published studies in adults and children found the combination had not demonstrated superior clinical efficacy compared with propofol alone. Studies conflicted regarding reduced hemodynamic and respiratory adverse effects with the combination compared with propofol monotherapy [203]. A comparison of propofol + ketamine to propofol + fentanyl for PSA in toddlers undergoing burn dressing changes found similar minimal impact on blood pressure and respiratory rate but less restlessness with the addition of ketamine [204].

Use of propofol for ED PSA should be preceded by specific training and supervised experience. It is recommended that when propofol is administered, an experienced provider with advanced airway skills be dedicated to administering the sedation and managing the airway and cardiorespiratory status of the patient. In-depth knowledge of adverse effects and advanced airway skills are essential for safe use of this drug.

Pharmacology

The exact mechanism(s) by which propofol exerts global CNS depression has not been fully elucidated. However, there is evidence that propofol potentiates $GABA_A$ receptor activity by slowing the channel-closing time, with lesser effects on $GABA_B$ receptors, modestly inhibits the *N*-methyl-d-aspartate (NMDA) receptor, modulates calcium influx through slow calcium-ion channels, and blocks sodium channels [205].

Pharmacokinetics [158]

Propofol is highly lipophilic and rapidly diffuses from plasma into body tissues, particularly the

highly perfused brain. The onset of action of propofol as determined by time to unconsciousness (i.e., loss of response to voice command) is within 1 arm-brain circulation time (the time required for the drug to travel from the site of injection to the site of action in the brain) and can be as brief as 15–30 s, but is more typically 40–60 s, dependent upon the rate of administration. Since propofol is rapidly distributed from CNS to inactive storage sites such as muscle and fat, recovery from anesthesia is rapid with duration of action about 5–10 min. The short duration of sedation after repeated doses can be explained by rapid metabolic clearance from blood and slow redistribution of the drug from the peripheral tissues. Thus, the pharmacokinetics of propofol after IV administration are best described by a 3-compartment model with rapid distribution of the drug from blood into the brain and other tissues, rapid metabolic clearance from blood, and slow redistribution of the drug from the peripheral compartment back into the bloodstream, resulting in sub-hypnotic plasma levels of drug.

Propofol is rapidly and extensively metabolized in the liver to less active conjugates which are excreted mainly in the urine. Since plasma clearance exceeds hepatic blood flow, it appears that the drug also is metabolized at extrahepatic sites. Mean total body clearance of propofol appears to be proportional to body weight; obese patients have a substantially higher body clearance than leaner individuals.

Indications: Propofol sedation of children in the ED has been reported primarily for fracture reduction with fentanyl, morphine, or ketamine coadministered [200–202, 206]. Sedation or distress scores were low during fracture reduction with propofol + morphine or fentanyl and similar to ketamine + midazolam or morphine + midazolam [201, 202]. Mean recovery times after propofol for these studies were 15–23 min. Unlike other PSA techniques, with the exception of nitrous oxide, repeated or continuous dosing of propofol causes little prolongation of recovery when administered for less than 1–2 h. Thus, after longer procedures such as complex laceration repair or emergent MRI scans during which either repeated doses or continuous infusion of propofol is required, recovery typically is still within 15–30 min [207].

Contraindications/cautions/adverse effects: Transient respiratory depression, apnea, upper airway obstruction, or laryngospasm may occur in many patients, especially during induction of sedation [86, 200, 208]. A recent study suggests that the administration of induction dosages of propofol slowly over 3 min decreases the incidence of respiratory depression [209]. Increasing upper airway narrowing due to muscle relaxation, especially at the level of the epiglottis, has been shown with increasing depth of propofol sedation/anesthesia [210]. Loss of protective airway reflexes during apneic periods may place patients at increased risk of pulmonary aspiration as the ensuing bag-mask positive-pressure ventilation increases gastric pressure and risk of passive regurgitation [86]. Therefore, candidates for propofol sedation must be carefully screened for risks of "full stomachs," URI's, and difficult airways [211]. These events are frequent enough when sedating with propofol that many providers routinely administer supplemental oxygen and monitor with end-tidal capnography, in addition to having a functioning anesthesia or CPAP ventilation bag at the bedside [105, 106, 115].

The main adverse cardiovascular effect of propofol is hypotension, in part related to decreases in peripheral vascular resistance [158, 212]. In spontaneously breathing patients, as much as a 30% decrease in blood pressure may be seen with little or no changes in heart rate [206, 213]. The decrease in blood pressure is dose and infusion rate-dependent and is potentiated by coadministration of opioids such as fentanyl [212, 214]. Propofol may rarely induce profound bradycardia and cardiac arrest in hypovolemic patients or in those at risk for hypotension or with cardiac dysfunction [86, 215]. Administration of additional fluids and a cautious rate of IV infusion may help reduce the risk of propofol-induced hypotension.

Because of the increased risk of apnea and hypotension compared to other agents for PSA, many providers avoid use of propofol in ED patients determined to have difficult airways,

cardiac dysfunction, brief fasting, or ASA Physical Status Classes 3, 4, or 5 [115, 200].

Propofol is formulated as an emulsion in soybean oil, glycerol, and purified egg products because it is essentially insoluble in aqueous solutions. Propofol therefore cannot be administered to patients with allergies to eggs or soy. In addition, to inhibit bacterial growth, some preparations contain sodium metabisulfite which may cause allergic-type reactions in susceptible individuals, including anaphylaxis and life-threatening or less severe asthmatic episodes [158].

Despite the addition of disodium EDTA or sodium metabisulfite to inhibit bacterial growth, significant bacterial contamination of open containers has been associated with serious patient infection. Using aseptic technique, propofol should be administered shortly after removal from sterile packaging [156].

Injection site pain is common with propofol but often may not be recalled due to propofol's amnestic effects. In ED PSA, coadministration of morphine or fentanyl for procedural analgesia may reduce this effect [115]. Lidocaine 0.5 mg/kg administered intravenously immediately prior to propofol infusion and use of large antecubital veins also may help ameliorate this minor adverse effect [158, 201].

Involuntary movement (myoclonus) has been reported in 15–20% of pediatric patients undergoing propofol anesthesia, typically during induction [158]. Myoclonus significant enough to interrupt the procedure, the majority of which were radiological, however, occurred only at a rate of 2/10,000 in elective sedations with propofol [86].

Dosages: Propofol can be administered intravenously in doses of 1–2 mg/kg to achieve sedation. Note however, administration of 2–3.5 mg/kg followed by continuous infusion of 100–300 μg/kg/min is commonly used for induction of general anesthesia [115, 200–202, 206, 216, 217].

Published studies of pediatric ED PSA for fracture reduction used an initial bolus of 1 mg/kg propofol administered over 1–2 min followed by additional doses of 0.5 mg/kg every 1–3 min based on patient response [200, 202, 206]. Mean total propofol doses in these studies were 2.5–4.5 mg/kg. Alternatively, one study followed the initial 1 mg/kg bolus immediately with a propofol infusion at 67–100 mg/kg/min until cast completion; most children required an additional bolus of propofol during the infusion to achieve the desired level of sedation [201]. In each of these studies propofol was administered shortly after morphine or fentanyl administration.

Administration: [158] Commercially available 1% propofol injectable emulsion (10 mg/mL) may be used without dilution. If dilution is necessary, the drug may be diluted with 5% dextrose injection to a concentration of not less than 0.2% (2 mg/mL) in order to maintain the emulsion. Propofol should be discarded if there is evidence of separation of the emulsion. The emulsion should be shaken well just prior to administration.

Using aseptic technique, contents of a vial may be transferred into a sterile, single-use syringe and administered shortly after removal from sterile packaging. The manufacturers state that propofol is compatible with several IV fluids (e.g., 5% dextrose, 5% dextrose and lactated Ringer's, lactated Ringer's, 5% dextrose and 0.2 or 0.45% sodium chloride) when a Y-type administration set is used.

Pregnancy category B

Etomidate

Indications: Etomidate has potent hypnotic (sedative) and amnestic but no analgesic effects. It is in an aqueous solution of propylene glycol therefore, burning on injection is a common complaint. Since etomidate rapidly induces unconsciousness with little hemodynamic effect and clinical recovery occurs within minutes, it is frequently used in the emergency setting to induce unconsciousness prior to neuromuscular blockade during endotracheal intubation [218–220].

Recent reports suggest etomidate may be safe and effective for brief nonpainful procedures such as CT scans and can be combined with fentanyl for fracture reductions. Early reports were inconclusive about the safety and effectiveness of etomidate for ED PSA in children [159, 221–224]. However, a small study of ED pediatric patients

sedated for head and neck CT found successful completion of the CT in 57% with etomidate doses up to 0.3 mg/kg and 76% with doses up to 0.4 mg/kg, in contrast to a success rate of 97% for pentobarbital [171]. Etomidate 0.2 mg/kg IV was infused over 30 s, with additional doses, if needed, of 0.1 mg/kg IV over 30 s at 1 min intervals, to a maximum total dose of 0.4 mg/kg. Duration of sedation was 13 min and parents felt their children returned to normal behavior much earlier than with pentobarbital. A more rapid infusion technique in another study reported a 99% successful completion of CT scans with etomidate in 446 fasted ASA-PS Class I, II children; duration of sedation was 34 min [225]. With a proximal tourniquet in place, 0.5 mg/kg lidocaine (maximum dose 25 mg) was first administered through the intravenous catheter to mitigate burning from the subsequent etomidate infusion, a "mini Bier block" technique. After 1 min, the tourniquet was removed and etomidate 0.3 mg/kg was infused over 2–3 s. If sedation was not adequate, an additional 0.15 mg/kg bolus was administered within 1 min of the initial dose. If needed, an additional 0.15 mg/kg bolus was given during scans requiring multiple views or repositioning. Median total etomidate dose was 3.3 mg/kg. With this technique, 1 patient had apnea and the CT scan was not completed, otherwise significant respiratory depression did not occur. Although most of these children were not ED patients, it suggests this agent may be used successfully for this purpose.

For fracture reduction, etomidate 0.2 mg/kg infused intravenously over 60–90 s resulted in effective sedation in 92% of children compared to 36% with midazolam 0.1 mg/kg IV [226]. Both were combined with fentanyl 1 μg/kg IV. Median recovery time in those reaching adequate sedation was 12 min with etomidate and 24 min with midazolam. Desaturation occurred in 22% of children in both groups; all responded quickly to free flow oxygen administration or head repositioning; no patient experienced apnea or required positive-pressure ventilation. Myoclonus occurred in 22% of patients who received etomidate but it was described as mild and brief and did not interfere with the fracture reduction. Pain on injection of etomidate was noted in 46% of children. Further studies of etomidate are needed to define better safety and efficacy parameters for PSA, particularly in unfasted emergency patients.

Contraindications/cautions/adverse effects: Similar to midazolam, transient apnea with rapid infusion may rarely occur when etomidate is administered alone [225] but respiratory depression may occur in 20% or more of children receiving etomidate coadministered with fentanyl or morphine [226]. Pain with injection in 2–20% and myoclonus in 8–40% of patients are associated with etomidate infusion [222, 227, 228]. When present, myoclonus that can resemble seizures usually lasts less than 1 min and can be decreased by the coadministration redundant of other drugs. These tremors are benign and not epileptiform activity [227, 229].

Although trials investigating etomidate-induced adrenal suppression associated with PSA in noncritically ill children are not available, studies in adults and children have demonstrated cortisol depression for up to 24 h with as little as a single dose of etomidate. This suppression may be clinically significant in patients with hemorrhagic or septic shock leading some to suggest consideration of alternative agents or to combine etomidate with glucocorticoids for induction of unconsciousness for tracheal intubation or PSA in these patients [230–233].

Pregnancy category D

Dosages: 0.2–0.3 mg/kg IV

Onset/duration: onset of sedation within 30–60 s, with duration of deep sedation 3–12 min when using a dose of 0.2–0.3 mg/kg [70]. Sufficient recovery for discharge may take 30–45 min [225].

Mechanism of action: Etomidate, like propofol, is structurally unrelated to other anesthetics. It is an imidazole derivative that is thought to induce sedation through enhanced gamma-amino butyric acid (GABA) neurotransmission [156].

Metabolization: Etomidate is highly protein bound in blood and is degredated by hepatic and plasma esterases to inactive products. It exhibits a bi-exponential decline, with a redistribution

half-life of 2–5 min and an elimination half-life of 68–75 min [156].

Sedative-Analgesic Agents

The following are primary analgesic agents. Sedation generally requires higher doses of opioids or addition of sedative-hypnotic agents, both of which significantly increase respiratory depression. Ketamine induces sedation and amnesia but opioid agents cause little amnesia.

Opiates (Narcotics) (Table 15.7)

Fentanyl (Sublimaze®)

Indications: Fentanyl is a high-potency synthetic opiate with minimal hemodynamic effects. Due to its lipophilic nature and rapid biphasic redistribution, onset of analgesia and sedation occur rapidly with intravenous administration but are of short duration, making it a favorable agent for ED PSA. Fentanyl, by weight, is 80–100 times more potent than morphine. It provides significant analgesia and mild sedation for painful procedures but is not recommended for anxiety control or for control of spontaneous movement. Since fentanyl, unlike morphine, does not cause clinically significant histamine release, it is the opiate of choice in patients who have increased potential for hypotension, e.g., trauma or sepsis [234].

Fentanyl has been administered in oral lozenges (oral transmucosal fentanyl citrate (OTFC)) for ED PSA for laceration repair. However, titration to effect is difficult with this technique and it has been associated with frequent nausea, vomiting (20–50%), and pruritus [235–238]. OTFC has also been used for rapid (30 min) analgesia in children with fractures [239].

Table 15.7 Comparison of opioid medications

Opioid	IV dose (mg/kg)	Peak	Duration
Fentanyl	0.001–0.002 (1–2 μg/kg)	30–60 s	30 min
Morphine	0.1	10 min	4–5 h
Meperidine	1	10 min	2–4 h

Of note, atomized intranasal administration of fentanyl in children in acute pain in the ED has been shown to provide significant pain relief by 5–10 min [240, 241]. One small study of children 1–4 years old undergoing suturing in the ED found intranasal sufentanil, a more potent analog of fentanyl, plus midazolam provided sedation by 20 min without vomiting or other significant adverse events [242]. Further study is needed to clarify safety and efficacy of atomized intranasal techniques for ED PSA.

Fentanyl plus Midazolam: A primary goal with most painful ED PSA is attenuated or blocked unpleasant recall of the procedure. Since fentanyl induces minimal amnesia and cannot completely block procedure-related pain without extreme respiratory depression, it is typically combined with midazolam to induce amnesia for residual procedural pain. Although the combination of fentanyl and midazolam can cause significant respiratory depression [96], both agents have competitive antagonists that readily reverse undesirable effects. If titrated carefully, a small dose of naloxone of 1 μg/kg will reverse respiratory depression but retain much of analgesia effect. This reversibility makes this combined technique an optimum and frequently used approach for ED PSA [159].

The dose of midazolam that maximizes amnestic effect is not well established. Furthermore, while the onset of peak amnestic effect is indistinct, the duration of action appears to be fairly long, hence a broad window within which to administer the analgesic agent, fentanyl. Thus, it is recommended to maximize the capability to administer sufficient amnestic agent by infusing the midazolam before the fentanyl is given since the synergistic respiratory depressant effects of the two medications may limit the ability to administer sufficient amnestic agent if it is given after the fentanyl.

Adequate analgesia for painful procedures always requires sufficient narcotic to cause some degree of respiratory depression (assuming narcotic naive patients). Use of local anesthesia for the procedure, e.g., a hematoma block for fracture reduction, can significantly reduce the amount of systemic analgesic agent needed and thus reduce respiratory depression. It is important

to time the "peak analgesia effect" (peak brain concentration) with "maximal analgesia need" (at time of the maximally painful part of the procedure), hence the analgesic agent is administered after the amnestic agent. The respiratory depression is typically counteracted by the pain of the procedure. Particular attention to ventilatory sufficiency should occur after the painful procedural stimulus ends, since respiratory depressant effects will persist for minutes to hours after the last dose of medication [122]. This adverse effect may be exacerbated by oral or parenteral opioid analgesics administered prior to the PSA.

Contraindications/cautions/adverse effects: Fentanyl, like other opioid analgesics, causes dose and infusion rate-dependent respiratory depression characterized by decreases in respiratory rate, tidal volume, minute ventilation, and ventilatory response to carbon dioxide. Hypotension and bradycardia may also occur with rapid infusion or larger doses. Although return to relative alertness typically occurs within 20–30 min after IV administration, respiratory depressant effects may last several hours. Patients may be awake but need to be reminded to breathe due to the drug's depression of the brainstem response to rising plasma CO_2 [118, 122, 243].

Respiratory depression can be lessened by administering the expected total dose in divided amounts, e.g., 0.5 μg/kg/dose, and infusing each dose over 30–60 s at 1–2 min intervals. Respiratory depression is markedly increased by coadministration of sedative-hypnotic medications such as midazolam or barbiturates [9, 96]. At the level of deep sedation, many children will have respiratory depression or partial upper airway obstruction due to muscle relaxation and may require airway opening maneuvers, supplemental oxygen, or painful stimulation [9].

Respiratory depression is readily reversed by the competitive antagonist naloxone. Titration of naloxone in small doses of 1 μg/kg stopping at the endpoint of reversal of respiratory depression will retain much of the analgesia effect. Repeated doses may be necessary as respiratory effects may outlast the reversal effects of naloxone. Administration of a "full" dose of naloxone may cause significant pain, hypertension, tachycardia, vomiting, and other undesirable adverse effects.

Chest wall rigidity may occur with rapid infusion of large doses (usually >5 μg/kg), especially in infants. This life-threatening adverse effect will manifest by lack of spontaneous chest wall movement, dropping oxygen saturations, and an inability to ventilate the patient with positive pressure by bag and mask. Reversal with naloxone or paralysis with succinylcholine may be needed to manage this adverse event.

Pregnancy category C

Dosages: *For analgesia*: 1–2 μg/kg, intravenously. Titrate to effect by administering doses of 0.5 μg/kg over 15–30 s, repeated every 1–2 min. A total dose of 1–2 μg/kg usually can be administered without causing significant respiratory depression, unless coadministered with midazolam. For significantly painful injuries, an initial dose of 1 μg/kg usually may be administered safely over 30 s.

For ED PSA: *Fentanyl + Midazolam*: Midazolam, 0.05–0.1 mg/kg intravenously over 1–2 min is administered first, titrated to an endpoint of drooping eyelids, slurred speech. A total dose of 10 mg likely is sufficient for amnesia in large adolescents. Then Fentanyl, 0.5 μg/kg intravenously over 30 s, repeat to an endpoint of decreased patient responsiveness to a relevant painful stimulus such as squeezing the fracture site or palpating the abscess. If local anesthesia is used for the procedure, approximately 1 μg/kg fentanyl may be sufficient. For intensely painful procedures, such as fracture reduction without a hematoma block, up to 2 μg/kg may be necessary [9]. Respiratory depression is likely at this dose therefore, time the end titration of fentanyl as the painful part of the procedure is begun; the procedure-related pain will stimulate the patient and counteract some of the respiratory depression. Additional doses of fentanyl may be administered after about 10 min if the patient becomes agitated or manifests significant pain during longer procedures.

Fentanyl comes in 2 mL vials of 50 μg/mL. Titration is easier and safer if the concentrated fentanyl is diluted to 10 μg/mL by adding 2 mL of fentanyl to 8 mL of normal saline, resulting in 10 mL of 10 μg/mL.

Onset/duration: Analgesia with mild sedation after IV administration of fentanyl is within 30–60 s with greatest sedative-analgesic effects lasting 5–10 min. Although return to relative alertness typically occurs within 20–30 min after IV administration, respiratory depressant effects may last several hours. Patients may be awake but "forget to breathe" due to the drug's depression of the brainstem response to rising plasma CO_2 [118, 122, 243].

Mechanism of action: Fentanyl is a high-potency mu agonist opiate 50–100 times more potent than morphine [234].

Metabolization: Fentanyl is metabolized in the liver and excreted in the urine. There are no active metabolites [234].

Morphine

Indications: While the "standard" for analgesia, morphine is typically not used for procedural sedation because its slow onset of peak analgesic effect (~10 min) makes titration difficult. Repeating a dose before 10 min leads to "stacking," i.e., administering a second dose before the peak effect of the first dose results in unnecessary excess medication administration, overshooting the intended level of analgesia, and is associated with excess adverse effects such as respiratory depression. Morphine is commonly administered to provide baseline analgesia if the patient is in pain from an injury, abscess, etc. Additional analgesia, typically with a different agent such as fentanyl or ketamine, is then administered for the procedure.

Contraindications/cautions/adverse effects: Additional administration of a benzodiazepine for anxiolysis increases the respiratory depression associated with morphine administration. Morphine induces histamine release and may result in hypotension, nausea/vomiting, dizziness, pruritus; histamine release may exacerbate asthma. Pruritus can be treated with diphenhydramine.

Dosages: IV: 0.05–0.1 mg/kg, titrated to the effect of pain relief. Opioid naïve patients may experience less nausea if the expected dose is divided. For example, an 80 kg teenager will likely better tolerate two 4 mg doses administered 10–15 min apart.

Onset/duration: 1–3 min, peak 10–20 min; duration of significant analgesia 1–2 h

Mechanism of action: mu agonist (analgesia), weak kappa agonist (respiratory depression).

Metabolization: glucuronidated in the liver and excreted in the urine: 10% metabolized to active metabolite which can accumulate in children with renal failure.

Pregnancy category C

Meperidine (Demerol®)

Indications: Although a potent opioid, meperidine, like morphine, is seldom used for procedural sedation because its long time to peak effect (~10 min) makes it difficult to titrate without overshooting (stacking) the intended level of analgesia and sedation. In addition, meperidine causes histamine release at a greater frequency than do other opioids and its atropine-like effects may cause tachycardia and euphoria.

Contraindications/cautions/adverse effects: Interaction with MAO inhibitors may be catastrophic resulting in hypertension, excitation, tachycardia, seizure, and hyperpyrexia. Biodegradation to the active metabolite normeperidine (elimination half-life of 15–40 h) results in prolongation of effects. With large or repeated doses, accumulation of normeperidine may cause nervous system excitation with tremors, muscle twitches, and seizures.

Dosages: IV/IM: 1 mg/kg.

Onset/duration: IV: 1–5 min, peak by 10 min; duration of 1–2 h.

IM: peak effect by 10 min, duration 1–2 h.

Mechanism of action: a phenylpiperidine opioid with potent analgesic effects.

Metabolization: hepatic degradation forms active metabolite normeperidine (elimination half-life of 15–40 h) which results in prolongation of effects and has adverse effects as noted earlier.

Pregnancy category C

Codeine

Codeine is well absorbed after oral administration but the drug must be metabolized by the liver to morphine to have an analgesic effect. Since up to 35% or more of people are slow or non-metabolizers, codeine is an ineffective analgesic

agent for many [244, 245]. Conversely, ultrarapid metabolizers may experience reduced analgesic effect but increased adverse effects from relatively small doses [246]. For these reasons, oxycodone is the oral analgesic of choice in the author's ED.

Oxycodone

Indications: Oxycodone, an opioid analgesic medication originally synthesized from opium-derived compounds, is readily absorbed by the oral route and is often administered for painful conditions when no IV access is established, e.g., at triage for possible fractures or burns [247]. It can also be used to augment sedation for painful procedures, e.g., with nitrous oxide for abscess I&D or fracture reduction [88]. Oxycodone is preferred because, unlike codeine, it does not require metabolism to an active form. Oxycodone may cause less nausea than codeine [2] but one comparison found no difference in vomiting or other adverse effects at analgesically similar doses [247].

Contraindications/cautions/adverse effects: Oxycodone, as do other opiates, significantly increases frequency of vomiting when combined with other analgesic regimens, e.g., with ketamine or nitrous oxide. Vomiting prior to ED discharge after PSA increased from approximately 10% with ketamine + midazolam [9] or nitrous oxide [10] to 25% when oxycodone had been administered in triage [88]. Oxycodone also causes dose-dependent respiratory depression by blunting the brainstem response to increasing levels of carbon dioxide. A dose of 0.2 mg/kg administered to children with painful injuries caused tiredness but no clinically apparent changes in ventilation or oxygenation [247]. At a dose of 0.3 mg/kg administered to young children in preparation for painful abscess I&D, we have observed many patients become sleepy but are easily aroused with verbal stimuli and oxygen saturations usually remain within normal ranges as they breathe room air; however, these children should routinely be monitored for respiratory depression after this larger dose.

Dosages: 0.05–0.15 mg/kg for out of hospital analgesia. *For procedural analgesia, 0.2–0.3 mg/kg,* with the larger end of the range for younger children for fracture reduction, burn debridement, or abscess management. Since absorption after gastric administration has large interindividual variation in the rate and extent of absorption [248], the higher dose is not recommended for home use due to the potential for oversedation. Similarly, oxycodone should be used with caution in infants younger than 6 months of age due to marked variation in clearance [249].

Onset/duration: Analgesia begins within 30 min, peaks at ~1 h; duration 2–3 h.

Mechanism of action: mu agonist (analgesia), weak kappa agonist (respiratory depression).

Metabolization: Oxycodone is metabolized by the cytochrome P450 enzyme system in the liver with up to 20% excreted unchanged in the urine. Thus, patients with poor renal function may accumulate higher plasma levels.

Pregnancy category B (D for prolonged use).

NMDA (*N*-Methyl-D-Aspartate) Antagonists

Ketamine (Ketalar®)

Ketamine is a phencyclidine derived lipophilic dissociative agent with rapid biphasic redistribution. Potent analgesic and amnestic effects with relative lack of cardiopulmonary depression make ketamine quite likely the most widely used and appropriate agent for ED PSA [159, 250]. The American College of Emergency Physicians (ACEP) has recently published a Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update [251]. The major changes in these guidelines as compared to the former of 2004, are summarized in the Fig. 15.4 [79, 251]. During fracture reduction, children receiving ketamine demonstrated significantly less distress and less respiratory depression than those receiving fentanyl or propofol coadministered with midazolam [9, 202]. Ketamine also induces significant amnesia and effective PSA for other intensely painful ED procedures such as burn debridement and abscess incision and drainage and relative immobility for procedures during which occasional spontaneous

General
- Expansion of guideline to include adults

No Longer Contraindications
- Administration for ages 3 to 12 months
- Minor oropharyngeal procedures
- Head trauma

Route of Administration
- Emphasis on IV over IM route when feasible

Coadministered Medications
- Routine prophylactic anticholinergics no longer recommended
- Routine prophylactic benzodiazepines may benefit adults but not children
- Prophylactic ondansetron can slightly reduce vomiting

Fig. 15.4 Major changes in the 2011 guideline (reproduced from Green et al. [251], with permission from Elsevier)

movement is tolerated, such as complex laceration repair and brief radiological procedures such as CT scans or joint aspiration [79, 159].

Ketamine has unique and diverse mechanisms of action with beneficial and potentially adverse effects. Ketamine interacts with multiple binding sites including *N*-methyl-d-aspartate (NMDA) and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic and opioid receptors, and less so, peripheral neuronal sodium channels [252]. Ketamine's primary site of anesthetic action is in the CNS in thalamocortical pathways and the limbic system where it binds to a site on postsynaptic NMDA channels which regulate transmembrane calcium, sodium, and potassium flux. This binding inhibits glutamate activation of the channel in a noncompetitive manner and is time and concentration dependent [119, 252, 253].

Circulatory Effects

In contrast to other sedative and analgesic agents, cardiac output, including heart rate and blood pressure, is usually well maintained with ketamine administration, even at deeper levels of sedation or anesthesia. Ketamine causes 10–30% increases in blood pressure and heart rate by blocking reuptake of catecholaminergic hormones norepinephrine, epinephrine, dopamine, and serotonin. These effects may increase intracranial pressure and caution has been suggested with its use in patients with known intracranial pathology causing increased intracranial pressure. However, use of ketamine in ventilated patients with head trauma has been shown safe and not to impact intracranial pressure differently from opioids [254, 255]. Use of ketamine in the ED for rapid sequence intubation of patients with head trauma has also been advocated as safe [256]. Of note, ketamine also has a direct negative inotropic effect on the heart that is usually clinically inapparent due to the sympathetic stimulation [257]. In critically ill patients whose catecholamines are depleted due to maximal compensation for hypovolemia, hypoxemia, fluid-electrolyte, acid-base, and other physiologic insults, administration of ketamine may cause marked hypotension and bradycardia [258].

Ventilatory Effects

In marked contradistinction to other sedative-analgesic agents, doses of ketamine typically used for ED PSA rarely cause depression of pulmonary gas exchange or relaxation of upper airway muscles [259]. Intravenous infusion of 2 mg/kg of ketamine over 1 min characteristically causes no significant effect on respiratory rate, tidal volume, minute ventilation, or end-tidal CO_2, thus maintaining adequate gas exchange during unobstructed spontaneous room air breathing [260]. Furthermore, ketamine does not significantly decrease thoracic or airway muscle activity [259, 261, 262], or impair lung ventilation distribution, functional residual capacity, or minute ventilation with intravenous doses of 2 or 4 mg/kg [134]. These effects and maintenance of positive end-expiratory pressure (PEEP) [263] result in lack of peripheral alveolar collapse and regional hypoventilation seen with propofol and opioid agents. Interestingly, relatively low-dose ketamine (1 mg/kg administered intravenously over 5 min, i.e., 0.2 mg/kg/min) to adults caused respiratory stimulant effects with three distinct phases: increased tidal volumes (deep breathing) was followed by increased respiratory rates and then large tidal volumes with low respiratory rates and occasional brief apnea, possibly compensating for hypocarbia due to the preceding hyperventilation [264]. These findings are consistent with the mild increase in respiratory rate

with maintenance of normal oxygen saturation and end-tidal CO_2 noted in children receiving intravenous ketamine 1.5 mg/kg over 1 min for ED PSA [111].

Reduced responsiveness to increased CO_2 and hypoxemia, however, have been demonstrated during the initial period after a bolus of ketamine when plasma levels are high and resolving as levels decrease [260, 265, 266]. This suggests the possibility of apnea in sensitive individuals or a delayed response to hypercarbia if airway obstruction occurs during induction of sedation and may explain the case reports of brief respiratory arrest after administration of intramuscular ketamine for ED PSA [120, 267, 268]. A case series of 18 children who inadvertently received 5–100-fold larger than intended doses of ketamine described respiratory depression and prolonged recovery but no residual effects except for one critically ill infant who died [157]. A meta-analysis of more than 8,000 children who received ketamine for ED PSA found that the overall incidence of airway and respiratory adverse events (upper airway obstruction, apnea, oxygen desaturation ≤90%, or laryngospasm) was 4%. Increased risk was found in younger children and teenagers, those receiving more than 2.5 mg/kg initial or 5 mg/kg total doses, and those receiving coadministered anticholinergic or benzodiazepine medications [137]. Airway and respiratory adverse events occurred at twice the overall rate in children younger than 2 years, except for laryngospasm or apnea which were not increased. The overall frequency of airway and respiratory adverse events in adolescents 13 years or older was almost 3 times greater with more apnea but less laryngospasm. The overall frequency of apnea was 0.8% in this series. Coadministration of other sedative-analgesic agents such as midazolam or morphine and young age also have been found by others to be associated with greater respiratory depression [87, 269].

Protective Airway Reflexes

Preservation of upper airway protective reflexes, even at deeper levels of sedation or anesthesia, reduces the risk of pulmonary aspiration and thus makes ketamine one of the safest agents for ED PSA in unfasted children, yet, paradoxically, it may increase the risk for one of the most significant life-threatening sedation related adverse events, laryngospasm [134–136]. The incidence of laryngospasm in ketamine-based pediatric ED PSA is difficult to determine as it is a rare event and large sedation databases are not available for estimation. The meta-analysis of pediatric ketamine-based ED PSA found an incidence of laryngospasm of 0.3%; the only identifiable association with greater risk was an initial intravenous dose of greater than 2.5 mg/kg but data was unable to be analyzed for URI, wheezing, or other risk factors noted with general anesthesia. Young age and oropharyngeal procedures (excluding endoscopy) were not associated with increased risk [137]. Although in the past, the prophylactic administration of anticholinergics were believed to reduce the incidence of secretions, laryngospasm, and respiratory complication, this is no longer held true. Rather, a recent matched case-control analysis of 8,282 ketamine procedures in the emergency department revealed no association between age, dose, procedure, medical status, route of delivery, and the administration of anticholinergics with the occurrence of laryngospasm [270]. This data is important because it identifies the occurrence of laryngospasm as an unpredictable and idiosyncratic reaction. All practitioners, thus, who administer ketamine should be prepared to identify and treat laryngospasm.

Initial management of laryngospasm should include airway opening maneuvers (straightening, jaw thrust) and administration of supplemental oxygen, preferably by continuous positive airway pressure (CPAP). If these are insufficient to maintain oxygenation, low-dose succinylcholine should be considered (~0.1–0.2 mg/kg IV); if this low dose does not improve oxygenation, a full paralytic dose of 1–3 mg/kg succinylcholine should be administered. Laryngospasm induced by ketamine may be brief or it may be recurrent and it may occur during emergence as well as induction or mid-procedure [133]. Please see section on "Management of Laryngospasm."

Sedative-Analgesic Effects

Sedation and dissociation induced by ketamine likely occur primarily from blockade of the excitatory effects of glutamate, the most prevalent CNS

excitatory neurotransmitter. By binding to the neuronal membrane's *N*-methyl-d-aspartate (NMDA) glutamate receptor complex associated with transmembrane calcium channels, ketamine prevents or reduces neurotransmission of pain and other stimuli by interfering with the calcium influx necessary for electrical propagation [252].

Dissociative Effects

Ketamine is classified as a dissociative general anesthetic agent because EEG and fMRI recordings demonstrate electrical activity of the thalamus that is no longer synchronized with or is "dissociated" from the limbic system after ketamine administration [271]. The thalamus is believed to process and relay sensory information selectively to specific areas of the cerebral cortex and plays a major role in regulating arousal, the level of awareness, and activity as well as processing auditory, somatic, visceral, and visual sensory input [135]. It is thought this dissociative effect is the primary mechanism for preventing patients' response to pain or other sensory stimuli after ketamine administration. More precise understandings of the mechanisms are under investigation. The patient who has received ketamine without an adjunctive sedative agent may have his eyes open but be unresponsive to the environment, described by some as if "the lights are on but nobody's home." This catatonic stare may be frightening to unprepared observers such as family members.

Prolonged Analgesic Effects

A relatively unexplored potential analgesic benefit of ketamine use for ED PSA is reduction of wind-up and central sensitization [272]. Brief noxious stimulation of peripheral tissue receptors initiates rapid neural transmission along myelinated and unmyelinated axons to the nerve's central terminus located within the dorsal horn of the spinal cord and induces release of excitatory neurotransmitters, primarily glutamate, into the dorsal horn synapse. The glutamate initiates rapid firing of postsynaptic AMPA and kainate receptors, resulting in sharp "first" pain and reflex withdrawal from the stimulus, soon followed by dull, aching, burning, and poorly localized "second" pain. Persistent noxious stimulation of these peripheral nerves induces pre- and postsynaptic neurons in the dorsal horn to undergo changes in function, chemical profile and structure that result in propagation of neural impulses at lower than normal thresholds, prolonged discharge, and widening of receptive fields. These changes have been termed "wind-up" and "central sensitization" hyperalgesia wherein successive similar stimuli cause increasing pain or normally subthreshold stimuli, such as light touch, produce intense pain at and adjacent to the site of original injury. Wind-up and central sensitization occur primarily by greater and more prolonged opening of postsynaptic NMDA channels to allow Ca^{2+} influx which reduces transmembrane potential and facilitates postsynaptic depolarization [273]. This central facilitation manifests within seconds of a nociceptive stimulus and can outlast the stimulus for hours, days, or longer if the stimulus is maintained, even at low levels [274, 275]. Experimental and clinical studies in adults have demonstrated that a single small dose of ketamine reduces the magnitude of hyperalgesia and windup-like pain [276–279]. Adults undergoing elective orthopedic or abdominal operations, for example, had reduced postoperative pain and marked reduction of opiate medication use for hours to days when as little as 50 mg of ketamine was added to their general anesthetic regimen [135, 280, 281]. Continued low-dose infusion of ketamine has also been shown to markedly augment morphine for analgesia after musculoskeletal injury in adults [282].

Paradoxically, opiates have been found to induce short-lasting analgesia and long-lasting hyperalgesia [283]. This opiate-induced hyperalgesia is also under the influence of excitatory neurotransmission and is similarly reduced by ketamine blockade of the NMDA-glutamate receptor [284–286]. Whether these prolonged beneficial effects occur with ketamine administration for ED PSA after an acute traumatic injury has yet to be explored.

Neurotoxicity

Concern has been raised about use of ketamine in children due to evidence of neurotoxicity in animals after high doses. Toxicity manifested as neuronal vacuolization has been found

within specific areas of the midbrain of rats after administration of 40 mg/kg ketamine, but not after doses of 5, 10, or 20 mg/kg [287]. Other investigators found no evidence of neuronal injury (apoptosis) in 7 day old rat pups after single doses of 25, 50, or 75 mg/kg; only with repeated injections of ketamine 25 mg/kg every 90 min for 9 h was any evidence of toxicity noted [288]. Of possible pediatric relevance, neuronal vacuolization was not found even with large doses of a potent ketamine-like drug (MK-801) in animals prior to puberty [289]. In addition, GABAergic drugs (e.g., diazepam) and alpha$_2$ agonists (e.g., clonidine) markedly reduce the excitotoxic effects of ketamine-like drugs; it has been suggested these should be coadministered with ketamine as a neuroprotective strategy [290].

A marked increase in normal CNS apoptosis or programmed cell death and some evidence of subsequent learning disabilities in association with administration of ketamine, ethanol, benzodiazepines, propofol, and volatile anesthetics also has been found in rodent animal models [291–293]. Of potential importance, the brain area most affected may vary by species. In rodents, key regions for learning are targeted whereas in the monkey, perhaps less essential cortical redundant cells are more affected [294]. While it is difficult to compare the effect of specific dosages across species, doses that achieve similar clinical effects as PSA have been shown to increase CNS apoptosis in infant mice [295]. Although ketamine has been used extensively in children without apparent ill effect, these studies raise serious concerns that are the targets of ongoing investigations.

Psychotomimetic Effects

Transient ketamine-induced schizophrenia-like symptoms including hallucinations, delusions, illogical thinking, poverty of speech and thought, agitation, disturbances of emotion and affect, withdrawal, decreased motivation, decreases in memory, and dissociation are well described in adults and a major constraint to use of the drug [296–299]. These symptoms occur when plasma levels of ketamine are relatively low and thus are seen during recovery from sedation. Similar to onset of schizophrenia, these symptoms are thought to be more common in adults and adolescents than in prepubertal children, but this has not been confirmed in children or in association with ED PSA [87, 253, 257, 300–302]. Dependent upon definitions, overall emergence phenomena are well tolerated and occur in approximately 5–25% of children recovering from ED PSA with ketamine, as well as with other drug regimens, and in similar frequency at home within days of discharge [9, 87, 301, 303]. However, significantly unpleasant and disturbing phenomena (i.e., nightmares, hallucinations, and severe agitation) occur unpredictably in approximately 5% or fewer children and are also seen with other drug regimens such as fentanyl plus midazolam [9, 87]. Midazolam routinely administered after ketamine or mixed within the same syringe does not appear to reduce significant recovery dysphoria and may increase agitation in postpubertal children [87, 304]. Of interest, preinduction anxiety and agitation have been correlated with emergence delirium for both ED PSA and general anesthesia [304, 305]. Whether pre-sedation midazolam for anxiolysis may reduce recovery dysphoria in significantly anxious children undergoing ED PSA, as has been shown with general anesthesia, is unclear [303, 306].

A potentially effective strategy to reduce emergence delirium, and one regularly employed by the author and others, is to inform the patient to expect transient funny dreams, diplopia, blindness, etc., and to have pleasant thoughts during induction of sedation [307].

Other Adverse Effects

Ketamine administration occasionally causes an evanescent erythematous rash shortly after infusion, and more commonly, double vision and dizziness during emergence from sedation, hypersalivation, typically with repeated or larger doses, and vomiting [9]. Vomiting in children who receive ketamine without adjunctive medications for ED PSA has been reported in 10–20% of children [87, 92]. Fortunately, vomiting almost always occurs during the recovery period and after discharge from the ED [9, 308].

Coadministration of opioids such as morphine or oxycodone increases emesis whereas coadministration of midazolam with ketamine significantly reduces the likelihood of vomiting (19 vs. 10%) [87] as does ondansetron (13 vs. 5%) [92]. Since vomiting may be more likely to occur in older children, ondansetron should be especially considered in children older than 5 years [92]. Vomiting does not appear to be linked to the length of pre-sedation fasting or the dose of ketamine administered [63, 90, 309].

Ketamine associated hypersalivation is thought to be mediated via cholinergic effects [135]. Because of concern that excess saliva may trigger laryngospasm and other adverse airway events, anticholinergic antisialagogues such as atropine or glycopyrrolate have traditionally been coadministered with ketamine [119, 253]. However, an unblinded observational study of approximately 1,000 children receiving intravenous ketamine without an antisialagogue for ED PSA, mean dose 2 mg/kg, found no significant hypersalivation or adverse airway effects [144]. In contrast, a randomized blinded trial of intramuscular ketamine, 4 mg/kg, with or without atropine, found increased salivation but no adverse airway events in those receiving ketamine [143]. These studies suggest hypersalivation may be dose related. Importantly, a meta-analysis found an increased occurrence of respiratory adverse events associated with antisialagogues [137]. Because of these studies and that "dry mouth" is a common complaint after atropine or glycopyrrolate, the author no longer routinely administers an antisialagogue when a single intravenous ketamine dose or total doses of 2 mg/kg or less are used for ED PSA.

Contraindications/cautions/adverse effects: (please see specific effects).

While much less common than with other ED PSA regimens, respiratory depression, apnea, and upper airway obstruction may occur with ketamine administration [268]. When identified by close monitoring and direct observation, these adverse effects are usually easily managed with simple maneuvers such as jaw thrust and airway straightening [308]. Ketamine preserves cardiac output in healthy patients but should be used with caution in patients manifesting shock as it may cause cardiac depression and profound hypotension [258].

Psychotomimetic effects, e.g., hallucinations, paranoia, and other schizophrenia-like symptoms, occur unpredictably and usually become manifested as dysphoria during recovery. Some believe these symptoms may occur more frequently in postpubertal children and in children with psychiatric disorders. Since the pathologic mechanisms of schizophrenia appear to be similar to ketamine induced effects, it is recommended to avoid use of ketamine in patients with psychiatric disorders and those whose close relatives carry these disorders. Although not well studied, children with attention deficit and hyperactivity disorders (ADHD) do not appear to have increased susceptibility to psychotomimetic effects. Ketamine is used routinely with and without midazolam in the author's ED for intensely painful procedures in adolescents; all verbal children are informed prior to sedation of what they might experience during recovery and given the suggestion to think of pleasant circumstances as sedation is induced. Midazolam routinely administered after ketamine or mixed within the same syringe does not appear to reduce dysphoria during recovery from ketamine sedation and may increase dysphoria in teenagers [87, 304]. Highly anxious children may benefit from receiving anxiolytic doses of midazolam well before ketamine, as has been shown with general anesthesia [306, 310, 311].

Ketamine is available in concentrations of 10, 50, or 100 mg/mL. For intravenous sedation, it is recommended only the 10 mg/mL concentration be used in order to reduce the risk of overdose and to facilitate titration to desired effect. It is also recommended that only one concentration be routinely available in the ED to reduce the likelihood that a more concentrated solution and thus, larger dose than intended, be inadvertently administered.

Pharmacokinetics

In unpremedicated children and adults, approximate ketamine distribution half-life is 24 s, redistribution half-life 4.7 min, and elimination half-life 2.2 h [312, 313]. The redistribution

half-life of 5 min is consistent with the typical deepest sedation period of 5–10 min observed with single dose ketamine for ED PSA. Midazolam or diazepam coadministration with ketamine may delay hepatic metabolism, yet it does not seem to prolong recovery although the midazolam sedative effects may prolong discharge [87, 314].

To reliably achieve the dissociated state for ED PSA, a minimum dose of ketamine 1.5–2 mg/kg administered intravenously over 30–60 s or 4–5 mg/kg administered intramuscularly are generally recommended [79, 251]. However, studies have found smaller intravenous or intramuscular doses to be effective, particularly when coadministered with midazolam [9, 88, 161, 315, 316]. Recent pharmacokinetic studies of ketamine ED PSA in children have helped elucidate why these different dosing strategies can be effective.

Age-specific ketamine pharmacokinetic profiles based upon measurement of plasma concentrations of ketamine in children 1.5–14 years of age who were undergoing ketamine ED PSA have been determined [317]. These profiles were then used to simulate several dosing strategies and recovery periods designed to achieve 15 min of very deep sedation/anesthesia (unresponsive or arouses, but not to consciousness, with painful stimulus) [160]. They predict, a typical 6-year-old child would recover (drowsy, eyes open or closed but easily arouses to consciousness with verbal stimulus) by 70 min after a 2 mg/kg infusion over 30–60 s. An alternative strategy of an initial bolus of 1.25 mg/kg with a subsequent half dose (0.625 mg/kg) "top-up" at 8 min would achieve recovery by 30 min. Finally, an initial dose of 0.3 mg/kg followed by an infusion of 3 mg/kg/h for 15 min would result in recovery by 20 min after the infusion was stopped. These and doses for other ages are listed in Table 15.8.

As with most drugs, between-subject variability has been found in ketamine effect and clearance. The mean target ketamine plasma concentration of 0.65 mg/L would only be effective in 50% of children; a concentration of 1.59 mg/L would be required to achieve a similar effect, with longer recovery, in 95% of children [160]. The rate of plasma clearance in children is similar to that in adults and correlates with hepatic blood flow. Clearance increases in a nonlinear function with decreasing age and is reflected by higher dose requirements (mg/kg) to maintain the desired effect in younger children. Size accounts for only about half of the clearance variability; it is unknown what impact pharmacogenomics add. In an individual child, titration to the desired depth of sedation must be gauged clinically.

Table 15.8 Ketamine dosing schedules to maintain very deep sedation levels for 15 min [160]

Age	Single dose (recovery ~70 min)	Intermittent dosing (recovery ~30 min)	Initial dose with 15-min Infusion (recovery ~20 min)
Adult	1.5 mg/kg	1 mg/kg + 0.5 mg/kg at 10 min	0.25 mg/kg + 2.5 mg/kg/h
12 years	1.75 mg/kg	1 mg/kg + 0.5 mg/kg at 8 min	0.275 mg/kg + 2.75 mg/kg/h
6 years	2 mg/kg	1.25 mg/kg + 0.625 mg/kg at 8 min	0.3 mg/kg + 3 mg/kg/h
2 years	2.125 mg/kg	1.5 mg/kg + 0.75 mg/kg at 8 min or 1 mg/kg + 0.5 mg/kg at 6 min + 0.5 mg/kg at 10 min	0.35 mg/kg + 3.5 mg/kg/h

Concern has been raised that very rapid intravenous administration of ketamine may increase the risk for apnea or marked respiratory depression, presumably due to rapid changes in brain ketamine concentrations [79, 251]. However, in the author's practice, small intravenous doses of 0.25–0.5 mg/kg administered over less than 5 s have not been associated with adverse respiratory effects and can provide effective PSA for procedures lasting for less than 5 min, such as simple fracture reductions or abscess incision and drainage (I&D).

Indications: Ketamine is particularly effective as PSA for intensely painful procedures such as fracture reduction, dislocated joint reduction, burn debridement, or abscess I&D [9, 159]. Ketamine

is also an effective PSA technique for brief painful radiological procedures such as guided joint aspiration or nonpainful CT scans, and repair of complex lacerations. Procedures that involve the oropharynx, such as peritonsilar abscess I&D, or endoscopy may be performed with light ketamine sedation (see case examples) but the sedating physicians must be prepared for an increased risk of laryngospasm [146, 318, 319].

Dosages: When administered in doses greater than 2 mg/kg, ketamine readily induces general anesthesia with unresponsiveness to painful stimuli yet with continued spontaneous respirations and good cardiac output. However, initial intravenous doses ≥2.5 mg/kg or total dose ≥5.0 mg/kg after repeated dosing have been associated with increased risk of adverse respiratory events [137]. It is recommended that ketamine be titrated to the desired degree of blunted response to intense pain. Complete lack of responsiveness to painful stimuli is unnecessary with ketamine as it is a potent amnestic agent [9, 79]. Providers and parents can be reassured (but not guaranteed) that most patients will have little or no memory of the painful procedure, even if moans occur during the most painful parts. It helps parents if providers confirm procedural amnesia by asking the patient what is remembered after recovery, especially when the parents have remained in the room during the procedure.

IV: (see Section "Pharmacokinetic") total dose 1–2 mg/kg when used alone is sufficient for the most intensely painful procedures lasting less than 5–15 min. If coadministered with midazolam, 1–1.5 mg/kg is often sufficient. The total dose can safely be administered as a single dose over 30–60 s but many sedators begin with an initial dose of 0.5 mg/kg administered over 15–30 s and repeated every minute until the desired blunted response to pain is achieved. For prolonged procedures, additional doses of 0.25–0.5 mg/kg may be administered as needed (about every 5–10 min), depending on individual patient response to stimulus [9, 315]. The smaller initial dose with additional doses as needed may shorten time for recovery [160]. Use of local anesthetics, when applicable, is highly encouraged to decrease the amount of ketamine needed. For an intensely painful but very brief procedure in which patient movement can be tolerated, e.g., moving a patient with a femur fracture off the spine board onto the ED bed, a small dose (0.2–0.3 mg/kg) administered rapidly by IV (over less than 5 s) can enable the patient to tolerate the procedure without losing consciousness; patients should be warned of feeling "weird" and monitored for possible sedation with this technique.

IM: 2–4 mg/kg, with smaller dose used for brief procedures in which local anesthesia is also used, e.g., laceration repair [316, 320].

Onset/duration:

IV: sedation-analgesia within 15–30 s with initial deeper effects lasting 5–10 min and recovery by 60 min, depending upon dose administered.

IM: sedation-analgesia within 5–15 min, duration 30–150 min, depending upon dose administered.

Metabolization: Hepatic degradation of ketamine within the cytochrome systems results in norketamine, which has one third the analgesic potency of ketamine. Norketamine has a shorter elimination half-life (1.13 h) than ketamine (2.1 h) [321].

Pregnancy category B

Adjuncts

Glycopyrrolate (Robinul®)

Indication: Antisialagogue is used by some clinicians before initial dose of ketamine. Preferred by some over atropine because it does not cross the blood–brain barrier thus, not causing possible undesirable CNS effects. Antisialagogues prior to single doses of 1–2 mg/kg of ketamine are likely unnecessary [137, 143, 144, 251]. It is unclear whether use of antisialagogues are beneficial in children with active URIs. Many children complain of "cotton mouth" for 6–8 h after glycopyrrolate administration [9].

Concentration: 200 μg/mL.

Dose: 5 μg/kg IV. Maximum dose is 200 μg. Administer at least 5–15 min before the initial dose of ketamine.

Atropine

Indication: Antisialagogue used by some clinicians in conjunction with initial dose of ketamine (instead of glycopyrrolate). Concern has been raised about potential CNS adverse effects with atropine, e.g., excitation, but this appears uncommon [143]. Antisialagogues prior to single doses of 1–2 mg/kg of ketamine are likely unnecessary [137, 143, 144, 251]. It is unclear whether use of antisialagogues are beneficial in children with active URIs.

Dose: 0.01 mg/kg (minimum 0.1 mg, maximum 0.5 mg).

Nitrous Oxide (N_2O)

Nitrous oxide (N_2O) is a colorless, odorless, and tasteless gas that, in a linear dose-response pattern, induces dissociative euphoria, drowsiness, anxiolysis, and mild to moderate amnesia and analgesia with onset and offset of effects within 2–5 min [322, 323]. N_2O is blended with oxygen (N_2O/O_2) and typically is described by the N_2O component, e.g., "70% N_2O" is 70% N_2O+30% O_2 [324]. At a specific concentration of N_2O, however, depth of sedation can vary considerably. One study of N_2O for ED PSA found 90% of children receiving 50–70% N_2O were mildly sedated (drowsy, eyes open or closed, but easily aroused to consciousness with verbal stimulus), whereas moderate or deep sedation occurred in 3% receiving 70% N_2O and in none receiving 50% [325]. Others report 2–10% of children may be poorly sedated during ED PSA with N_2O [10, 325, 326].

Since N_2O sedation and analgesia are usually mild to moderate, children are partially aware and strategies to enhance the gas's anxiolytic, dissociative, and euphoric effects are vital to successful use for PSA. Guided imagery significantly augments N_2O's efficacy and helps allay anxiety [323, 327]. Children naïve to intoxication are frequently frightened by the floating or tingling sensations caused by the gas, but they readily accept these effects when incorporated into non-frightening scenarios. The author often encourages preschool and school-aged children to imagine flying to a favorite or imaginary place, "soaring with eagles, past clouds and stars to check out the moon," guiding the child during the sedation by detailed descriptions of what might be "seen" along the way. Alternatively, some children like describing their own imaginings, allowing the author to figuratively "tag along," as with a 5-year-old girl who portrayed in great detail her "chocolate ponies" as her radius fracture was being reduced. Finally, some older children and teenagers prefer the partial awareness with N_2O sedation as they, like many adults, fear loss of vigilance or control associated with potent sedation or anesthesia.

Effective pain reduction by concurrent use of local anesthesia and/or systemic analgesia for painful procedures is also crucial for successful N_2O ED PSA [328]. For examples, forearm fractures can be reduced with minimal distress when N_2O sedation is augmented by a lidocaine hematoma block [88, 329, 330], or lacerations repaired calmly in young children when they have also received topical anesthetic [10]. The lack of painful administration or need for venous access and the rapid onset and offset of effects make N_2O ED PSA an attractive option for many clinical situations.

N_2O can safely be administered by specially trained nurses to healthy children for ED PSA [62, 331, 332].

Indications: N_2O, along with local anesthesia and/or oral analgesics, primarily is used for anxiolysis, mild analgesia and amnesia during brief (<5–10 min) procedures, such as laceration repair, abscess incision and drainage, lumbar puncture, IV placement, and some fracture reductions. Use of 60–70% N_2O or coadministration of opioids or sedatives may deepen sedation and improve efficacy [129–131]. The author frequently administers oxycodone 0.2–0.3 mg/kg orally 30–60 min prior to N_2O sedation for I&D of an abscess in toddler and preschool children. Although seldom seen, these children are monitored for respiratory depression before, during, and after the sedation.

Many find the gas more effective in children old enough to cooperate and use imagination, but significant reduction of procedure-related distress

has been observed in 2 year old and younger children [10]. In the author's ED, N_2O sedation is regularly used effectively in infants of 3 months of age and older by administering with a continuous-flow system, described later.

Suturing-related distress in children can be reduced by N_2O [10, 326, 333–335]. We found 2–6 year old children who had received topical anesthetic and were viewing cartoons with a parent at the bedside, had less distress during wound cleaning, supplemental lidocaine injection, and suturing if receiving 50% N_2O instead of oral midazolam. Children who received N_2O alone recovered rapidly without ataxia or dizziness, but did have more vomiting (10%) [10]. Of note, 30% N_2O was found insufficient in children younger than 8 years old in another study [333].

Mid to distal forearm fracture reduction can be effectively performed with N_2O sedation, particularly when combined with a local anesthetic hematoma block [88, 329, 330, 336–338]. We found N_2O plus 1% lidocaine hematoma block (2.5 mg/kg, maximum 100 mg) as effective as intravenous ketamine in reducing distress during fracture reductions in children aged 5–17 years. This technique is often most effective in displaced mid to distal forearm fractures which have large fracture site hematomas that enable effective hematoma blocks, whereas, torus or green-stick fractures that require reduction likely have small or no fracture hematomas making the lidocaine block less effective; an effective fracture hematoma block is the key for maximum success. For these incomplete fractures, hematoma blocks may provide partial pain relief and, combined with 70% nitrous oxide along with prior oral oxycodone or other potent analgesic, enable many children to tolerate fracture reduction with acceptable distress. The child usually recalls less pain related to the fracture reduction performed with N_2O sedation than an observer would expect based upon the child's response during the procedure [329]. It is usually reassuring to ask the child after recovery, with the parent(s) present, what he or she recalls of the procedure, especially when the parent was present during the reduction and the child had manifested some distress. Recovery is markedly faster from N_2O compared to ketamine-based sedation for fracture reduction (16 vs. 83 min) [88]. If the N_2O is turned off as soon as any painful moulding of the cast at the fracture site after reduction is completed, the patient is typically recovered to near baseline before the casting or splinting is finished.

Children's distress during other painful ED and outpatient procedures such as lumbar puncture, abscess drainage, dressing change, and intravenous catheter placement likewise can be reduced by N_2O [325, 335, 339–344]. Recovery from N_2O sedation typically is very rapid, with the child able to sit alone within 5 min and ready for discharge within 15 min [76].

Technique: As described previously, successful N_2O sedators engage the child in imaginative stories throughout the procedure. Distraction, imagery, and storytelling significantly enhance desired effects by giving the child a nonthreating construct in which to place the sensations caused by the gas. While breathing N_2O, children are able to follow commands, describe sensations of floating, frequently laugh, and occasionally chew or lick masks that have been scented with bubblegum spray or flavored lip-balm to enhance acceptance of the mask. Adolescent and school-aged children often begin giggling if it is suggested to them that this is expected and their parents typically also begin laughing when this occurs, presumably easing their own anxiety. Coaxing children as young as 2 years of age to hold the mask on their face adds a measure of safety by allowing them to remove the mask quickly if vomiting occurs. Their ability to hold the mask also indicates their depth of sedation and may reduce anxiety related to the mask covering their mouth/nose. When the mask is held in place by a sedator, that person must be vigilant for evidence of vomiting and quickly remove the mask to allow the child to clear the emesis.

Titration of the gas beginning at 30%, the anxiolytic dose, and increasing the concentration to 50–70% over 2 min may reduce children's fear during induction. Others find when children have been prepared with explanations about what effects they are likely to feel, they tolerate beginning at 50–70%. With either technique, the child should breathe the maximum concentration

desired for 1–2 min, allowing full effect, before beginning the procedure.

Administration of 100% oxygen after cessation of N_2O to prevent "diffusion hypoxia" is unnecessary unless the patient is emerging from deep sedation or general anesthesia. N_2O diffusing from the bloodstream into the alveoli and displacing oxygen is readily exhaled without causing hypoxia in patients recovering from sedation with N_2O alone [128, 345, 346]. As with any sedation technique, children should be monitored with pulse oximetry until alert, usually less than 3–5 min after ending N_2O administration.

Delivery system: Until recently, delivery of N_2O (fixed at 50%) in the ED has been by demand-valve systems designed for adult use (Nitronox/Entonox®). Children have difficulty generating the negative inspiratory pressure required to initiate gas flow with these devices. Continuous-flow systems, such as those used by dentists, oral surgeons, and anesthesiologists, in contrast, provide free flow of gases with the ability to deliver up to 70% N_2O. These systems allow normal respirations and are easily used by patients of all ages [324, 347]. Dental systems with nasal hoods can be adapted for use with a full face-mask by adding into the expiratory limb an open gas interface designed for anesthesia machines. N_2O concentration is limited to a maximum of 70–75% as concentrations exceeding 79% (+21% O_2) would cause hypoxia. Accidental administration of 100% N_2O due to machine or system failure can be rapidly lethal [154, 348, 349]. Providers must be very familiar with the mechanisms of the N_2O delivery system used. A machine or systems check should be performed before each use of N_2O to assure proper function of the machine and monitors.

A scavenging device should be an integral part of the delivery system to minimize ambient levels of N_2O gas exposure to healthcare workers since chronic and repeated exposure to N_2O may cause abnormalities in hematologic, neurologic, and reproductive systems (see cautions). The N_2O delivery device and the treatment area in which it is used should be in compliance with National Institute of Occupational Safety and Health Standards and state safety guidelines and regulations [350]. It is beneficial to have room air exchanges of at least 10–20/h in treatment rooms to remove any N_2O that has escaped the scavenging process.

Monitoring: An in-line oxygen analyzer should be used to assure proper equipment functioning/adequate oxygen delivery during N_2O administration [154]. A gas analyzer that measures inspiratory and expiratory N_2O and end-tidal CO_2 concentrations adds additional assurance of patient safety and equipment function.

Administration of ≤50% N_2O, without any other sedative, narcotic, or other respiratory depressant drug, to children ASA-PS class I or II, is considered minimal sedation and the patient may be monitored by direct visualization and intermittent assessment of their level of sedation [154]. The child should be able to be verbally interactive throughout the sedation. If >50% N_2O is administered or if the patient receives concurrent narcotic or other sedative drugs, the patient should be observed closely for moderate sedation and monitoring should escalate accordingly with pulse oximetry, etc. Since oxygen is blended with N_2O, even mild hypoxemia is very unlikely and should cause immediate investigation to determine the cause.

Contraindications/cautions: At normal atmospheric pressure, N_2O cannot induce general anesthesia, unless combined with other agents. N_2O at 30–70% has been safely used widely for more than a century to reduce distress in children during dental procedures [351]. Review of nearly 36,000 administrations of 50% N_2O for non-dental procedures, 82% of which were in children, found 9 (0.03%) serious adverse events (somnolence, vomiting, bradycardia, vertigo, headache, nightmares, sweating) that may have been attributed to the N_2O [352]. In healthy patients (ASA-PS I, II), N_2O has minimal cardiovascular or respiratory effects [76, 130, 345]. N_2O, however, may enhance the depressed response to hypoxia and hypercarbia induced by other agents [129–131, 325, 353].

N_2O diffuses rapidly into air-filled cavities causing volume and or pressure increases proportional to concentration and duration of N_2O inhaled. Therefore, N_2O should not be administered to patients with areas of trapped gas such as pneumothorax, obstructive pulmonary disease, or

bowel obstruction. Albeit seemingly rare, patients with acute otitis media may experience painful increase in middle ear pressure. Other relative contraindications include significant head injury (N_2O mildly increases intracranial blood flow), altered mental status, and psychiatric disorder (N_2O may cause dysphoric effects similar to ketamine).

Bone marrow suppression, liver, CNS, and testicular dysfunction, decreased fertility and increased spontaneous fetal loss, and peripheral neuropathy may possibly occur with repeated and chronic exposure [76, 324]. None of these adverse effects have been found when scavenging devices are integrated into the system. Therefore, use of a scavenging device is essential to minimize ambient levels of gas and exposure to healthcare workers.

Deaths associated with N_2O use have been due to inadvertent administration of 100% nitrous oxide, with subsequent hypoxia [348, 349]. These occurrences primarily were in patients already sedated with other drugs as part of anesthetic regimens. These tragedies point out the essential need for clinicians to understand all aspects, including mechanical, of the gas delivery device being used.

Pregnancy category C

Adverse effects: Vomiting occurs in approximately 10% of children receiving 50% N_2O, along with transient dizziness and headache in some [76]. These effects usually resolve within 5 min of cessation of N_2O administration. Vomiting frequency increases with opiate and decreases with midazolam coadministration [10, 88]. Some providers believe the risk of vomiting increases when the duration of administration exceeds 5–10 min, especially with greater than 50% concentrations, but this is yet to be substantiated. Whether antiemetics such as ondansetron reduce N_2O induced nausea and vomiting is unclear. Protective airway reflexes are largely intact when N_2O is used alone [354–356]. Whether combining N_2O with other sedatives or analgesics increases risk for aspiration and other adverse events is unknown but the risk likely correlates with the patient's depth of sedation and effects of the coadministered drug.

Dosages: Concentrations of 30–50%, blended with oxygen, achieve Minimal to light Moderate sedation in most children without adverse cardiopulmonary effects [76]. More recently, routine use of 60–70% has been recommended and found safe in children undergoing sedation in the ED [325]. In the author's ED, 50–70% concentrations are typically used with initial higher concentrations and then reduced as the most painful part of the procedure is accomplished.

Onset/duration: Patients experience the effects of N_2O within 1 min but for optimum effect they should inhale the gas for 2–3 min before beginning a procedure to allow brain concentrations to equilibrate with the delivered concentration of gas. Recovery occurs rapidly with children being able to sit alone by 3–5 min after cessation but initially they should be assisted with walking as ataxia may occur for a bit longer.

Mechanism of action: N_2O has *N*-methyl-d-aspartate (NMDA) glutamate receptor antagonist, opioid agonist, and GABAergic effects [357–359].

Metabolization: N_2O is excreted unchanged by exhalation.

Ketamine+Midazolam or Fentanyl+Midazolam Techniques for Deep Sedation

Providers utilizing these regimens should be thoroughly familiar with these medications and sedation guidelines outlined in text. Sedation should be performed in an area fully equipped for resuscitation.

Pre-Sedation Assessment and Preparation

1. Initial assessment: determine patient's ASA classification, airway risks, time of last oral intake, obtain informed consent.
2. Establish indwelling venous access maintained with normal saline or Ringer's lactate.
3. Attach patient monitors to continuously measure patient's oxygen saturation (with variable

pitch indicator), heart rate, and respiratory rate and intermittently measure blood pressure. Consider pre-oxygenation and supplemental oxygen delivery during the sedation if capnography if available and staff trained in use.
4. Prepare positive-pressure ventilation bag and mask, assure ability to deliver supplemental oxygen.
5. Prepare oral suctioning device with rigid tip.

During Sedation

1. Assign a provider whose sole responsibility is to monitor patient safety.
2. Continuously monitor patient by direct observation, oxygen saturation (with variable pitch indicator), HR, RR, and monitor blood pressure after each medication infusion and at 5-min intervals. Patient monitoring and direct observation at increasing intervals is continued during recovery until discharge criteria are met.
3. Infuse medications near the hub of the catheter over 10–20 s, in small incremental doses to titrate to desired endpoint of analgesia, sedation. Use of dilute solutions and precalculated dosage tables based upon patient weight is recommended.
4. Administer medications intravenously when supportive staff present and prepared to render support if necessary and provider to perform procedure prepared to begin.

Fentanyl Technique

(a) Midazolam: 0.05–0.1 mg/kg (0.05–0.1 mL/kg) at 2–3 min intervals; endpoint: decreased patient anxiety, mildly slurred speech, drooping eyelids; typically effective dose: not more than 0.1 mg/kg to induce marked amnesia along with sedation. Then
(b) Fentanyl (10 μg/mL): 0.5 μg/kg (0.05 mL/kg) at 2–3 min intervals; endpoint: decreased patient responsiveness to painful stimulus or decreasing oxygen saturations; typically effective dose: 1–1.5 μg/kg.

Ketamine Technique

(a) Midazolam may be reserved for anxious patients undergoing ketamine sedation. For anxiolysis, dose: 0.05 mg/kg, maximum dose: 2 mg, single administration 5–15 min prior to initiation of sedation.
(b) Ketamine (10 mg/mL): dose: 0.5–1 mg/kg (0.05–0.1 mL/kg) at 1 min intervals; endpoint: decreased patient responsiveness to painful stimulus; typically effective dose: 1–2 mg/kg. Supplemental doses of 0.5 mg/kg may be administered as indicated by patient distress.

Consider using an antisialagogue, e.g., glycopyrrolate 5 μg/kg or atropine 0.01–0.02 mg/kg, prior to ketamine administration if it is an anticipated procedure will require multiple supplemental doses of ketamine.

Caution: Suggested doses may readily result in oxygen saturation falling below 90% in patient's breathing room air, particularly when fentanyl is used. Providers must be prepared to immediately turn the patient to his side if vomiting, reposition or suction patient's airway, provide supplemental oxygen or positive-pressure ventilation until patient has returned to baseline physiologic status and recovered from sedation.

Final Thoughts

This chapter has presented the sedation provider with a range of sedation techniques and options for painful and non-painful procedures which may need to be performed on an urgent basis. There is no doubt that sedation and analgesia are important components of the emergency department care and should be an integral component of the emergency medicine physician's practice. The training and credentialing process for sedation is an area of recent interest from the American College of Emergency Physicians. In July 2011, the American College of Emergency Physicians released a Policy statement entitled Procedural Sedation and Analgesia in the Emergency Department: Recommendations for Physician Credentialing, Privileging, and Practice [362]. This Policy iterated that the chief of the emergency medicine service at each institution will be responsible for establishing criteria for credentialing and recommending emergency physicians for sedation privileges. Sedation training should "focus on the unique ED environment". This

Policy is important, because it empowers the chief of emergency medicine with the responsibility of establishing sedation training and credentialing requirements for the emergency medicine specialty. Furthermore, the Policy expands the role of the emergency physicians as well as emergency medicine nurses by condoning the capability of qualified ED nurses to "administer propofol, ketamine, and other sedatives under the direct supervision of a privileged emergency physician". The Policy also recognizes that there may be occasions whereby the emergency medicine environment may not lend itself to having a separate physician administer the sedative and another to perform the procedure: For these situations, the Policy states "Deep sedation may be accomplished…..by the same emergency physician both administering sedation and performing the procedure".

As the practice of sedation evolves, one can anticipate that the American College of Emergency Physicians will continue to survey the landscape, evaluate the literature and recommend policies and guidelines to promote the safe and efficacious delivery of sedation in the emergency medicine environment.

Case Studies

Case 1

A 12 year-old boy has closed *displaced metaphyseal fractures of his distal right radius and ulna* and numbness in his 3rd and 4th fingers. He fell 30 min ago running in gym class and has no other injury. He takes methylphenidate for attention deficit-hyperactivity disorder. He otherwise is healthy and has never received sedation or anesthesia. He ate lunch 2 h prior to arrival and was given ibuprofen by his mother on the way to the hospital. He is anxious and crying in triage.

Issues: Pain relief now and during radiographs and exams; PSA for fracture reduction with consideration of his fasting status, anxiety, ADHD, and neurovascular status of his injury.

1. *Pain relief* will facilitate imaging of the fractures, accurate assessment of the injury, and preparation of the patient for PSA for fracture reduction. Options include:
   (a) *Splinting* the injured area to prevent movement of the fractured bones provides significant pain relief.
   (b) *Systemic analgesia*: Administer before radiographs, even if the child indicates less pain after splinting. Repositioning of the injured limb for radiographs and subsequent exams will be quite painful. Options include:
   (i) *Oxycodone orally*: In our ED, nurses follow standing orders to administer a first dose of oxycodone 0.2 mg/kg orally (maximum dose 10 mg) in triage to children with a potential isolated extremity fracture or other painful injury. This allows rapid and effective attention to the reduction of pain and high patient, family, and staff satisfaction. Noticeable analgesia occurs by 20–45 min with peak effect by an hour and with duration of 2–4 h. This dose is unlikely to cause sedation in children with painful injuries. Doses for home use are 0.05–0.15 mg/kg. Oxycodone is preferred over codeine because it does not require metabolic conversion for analgesic effect. Codeine is slowly or poorly converted to morphine in 2–40% of patients and thus

provides poor or no pain relief to such children. If codeine previously has been effective for a specific child, a first dose of codeine 2 mg/kg orally is effective for these painful injuries with subsequent or home doses of 1 mg/kg.

(ii) *Fentanyl intranasally,* 1.5–2 μg/kg, achieves significant pain relief within 5–10 min with duration of 30–90 min. Use atomizer to spray small volumes of concentrated intravenous fentanyl solution (50 μg/mL) to improve absorption. Divide total dose into repeated sprays of ~0.1–0.2 mL/nostril. Use of small volumes reduces drainage of drug into posterior pharynx where it is less absorbed. If a wide margin of safety is determined after more extensive use of this technique, it might be performed by nurses in triage, but currently it is performed by a physician in a treatment room with patient monitoring for respiratory depression.

(iii) *Opioids intravenously* titrated to effect will provide the greatest pain relief. Fentanyl 1–2 μg/kg IV will provide analgesia within 1–2 min, lasting 30–60 min, whereas morphine 0.1 mg/kg IV will provide initial analgesia within 5–10 min with peak effect at 10–20 min and lasting 2–3 h. This strategy requires IV insertion, typically in a treatment room after physician assessment and orders. Anxiety and pain associated with catheter insertion are significant for many children and are greatly reduced by use of local anesthesia such as buffered lidocaine injected subcutaneously via a 30 gauge needle at the site of insertion.

(iv) *Nitrous oxide 50–70%* provides rapid pain relief. However, because continued analgesia requires ongoing administration and N_2O scavenging systems are not mobile, a longer acting systemic analgesic usually is needed. One strategy is to use N_2O to reduce the patient's pain and distress while an IV catheter is inserted for subsequent opioid administration. This strategy typically requires physician assessment and orders, access to N_2O, and IV catheter insertion in a treatment room.

2. *Fasting status*: This child ate lunch 2 h prior to his arrival. Pain from injury and opioid analgesics unpredictably slow intestinal motility. It is uncertain if delaying sedation for 2–4 h in these patients will allow significant additional gastric emptying. Vomiting with PSA does not correlate with the length of fasting. Furthermore, ED PSA does not involve tracheal intubation, a procedure that significantly increases risk of pulmonary aspiration during general anesthesia. Of note, pulmonary aspiration has not been reported in children undergoing ED PSA, despite most being incompletely fasted. As with general anesthesia, no studies have determined if pulmonary aspiration risk is reduced in non-fasted patients by pre-sedation administration of medications to enhance gastric emptying, inhibit gastric acid production, or decrease pH of gastric contents and such strategies are not recommended. The author's practice is to use PSA techniques that preserve airway reflexes as described herein, to be prepared for vomiting in all patients, and to perform PSA when the full complement of providers is available to perform the procedure and monitor the patient.
3. *PSA techniques*: Since this non-fasted patient has potentially increased risk of pulmonary aspiration of gastric contents, a

sedation technique that better preserves protective airway reflexes may increase patient safety. Ketamine and N_2O are NMDA receptor antagonists that blunt protective airway reflexes less than the opioid and GABAergic agents such as fentanyl, midazolam, and propofol.

(a) *Nitrous oxide* (*50–70%*) *plus lidocaine fracture hematoma block,* along with oxycodone administered at triage, is as effective in reducing distress associated with fracture reduction as intravenous ketamine, provided an effective hematoma block is placed. To reduce risk of nerve and vascular injury from injection, hematoma blocks are typically reserved for mid to distal forearm, and, occasionally, ankle fractures. We administer 50% N_2O to the child as the orthopedic surgeon, using sterile technique and a dorsal approach, injects 1% buffered lidocaine (2.5 mg/kg or 0.25 mL/kg, maximum dose 100 mg or 10 mL) into the fracture hematoma. N_2O 70% is usually administered for the subsequent fracture reduction. Aspiration of hematoma blood into the lidocaine-containing syringe confirms proper location of the needle for injection. Perhaps counterintuitively, the worse the fracture, the more effective is fracture site anesthesia due to larger hematomas. The provider must be prepared for as yet unreported but potential seizure or dysrhythmia due to rapid intraosseous absorption of lidocaine. This theoretical risk is low since the injected lidocaine is within the drug's therapeutic dose range. Some orthopedic surgeons prefer not to use this technique if the fracture and swelling cause numbness in the hand, typically median nerve distribution, because of inability to reassess nerve function immediately postreduction. Use of lidocaine instead of longer acting local anesthetics such as bupivacaine enables postreduction neurologic assessment within 1–2 h. Variable patient awareness is present with N_2O PSA, thus distraction and guided imagery are crucial to improve efficacy of this technique. Some older children and teenagers, as many adults, prefer not to be unconscious during a procedure if pain is sufficiently reduced.

(b) *Ketamine I.V. with or without Midazolam* more effectively reduces patient distress during intensely painful procedures and causes less respiratory depression than fentanyl or propofol-based techniques. Intravenous administration is preferred because multiple attempts likely will be needed to align both the radius and ulna, thus increasing potential need for additional doses of ketamine. Time of recovery is reduced by administering a smaller initial dose followed by a half dose. For a child of this age, an *initial ketamine dose 1 mg/kg followed by 0.5 mg/kg at 8 min* likely results in approximately 15 min of very deep sedation with recovery to drowsiness and easy arousal by verbal stimulation by about 30 min. If longer deep sedation is needed for repeated reduction attempts, additional dose of 0.5 mg/kg can be given as needed. Alternatively, an initial ketamine dose of 1.75 mg/kg will result in 15 min of deep sedation but recovery likely will take 60–70 min.

Intramuscular ketamine 4 mg/kg provides effective PSA without vascular access but additional doses, if necessary, will require 4–5 min to determine if sufficient. Recovery is significantly longer than with intravenous ketamine and vomiting is more frequent (26 vs. 12%). Ability to obtain vascular access emergently (intraosseous, if necessary) must be present to manage life-threatening adverse events should they occur.

Midazolam 2 mg total dose may reduce the child's anxiety as preparations are made for PSA. Although yet unconfirmed with PSA, reduced anxiety at induction correlates with reduced dysphoria during recovery from general anesthesia. This small dose is not likely to cause respiratory depression or prolong recovery. Midazolam administered in the same syringe or immediately after ketamine does not appear to reduce recovery dysphoria.

Glycopyrrolate or atropine to reduce ketamine associated increased salivation are recommended by some to reduce the low risk of laryngospasm. Hypersalivation is usually not significant with these doses of ketamine but may occur with repeated doses for prolonged procedures. The author no longer routinely administers an antisialagogue because these agents have been associated with increased likelihood of adverse respiratory events, and patients complain of dry mouth after recovery.

Vomiting: Administration of opioids such as morphine or oxycodone with ketamine increases emesis (10 vs. 25%) whereas, administration of midazolam decreases vomiting (19 vs. 10%) as does ondansetron (13 vs. 5%).

Cautions: Although unlikely to occur, providers must be prepared for hypoventilation, apnea, or laryngospasm with ketamine. As with all deep sedations, this child must be monitored for adverse effects by an experienced dedicated provider during induction, sedation, and recovery. If vomiting occurs, the procedure immediately is interrupted and the child turned to his side to assist his clearing emesis. Observers, e.g., parents, should be forewarned about nystagmus and catatonic stare during sedation and possible dysphoria during recovery. Similarly, patients should be prepared for possible diplopia, dizziness, hallucinations, and a brief period of blindness during recovery. Getting the child to focus on pleasant thoughts during induction and recovery may reduce some of these psychotomimetic effects. Most patients will have no memory of even intensely painful procedures, even if they occasionally moan, but some will have partial recall, usually quite vague. It may help reassure observers if the child indicates no recall when asked after recovery.

(c) *Fentanyl + Midazolam or Propofol* provides effective PSA but blunts protective airway reflexes more than ketamine. This child's recent food intake makes these techniques less desirable. It is unknown whether delaying PSA will improve gastric emptying. Please see *Fasting Status* mentioned previously.

(d) *Reduction under general anesthesia* may be considered. However, reduction should not be delayed long because of the apparent median nerve impingement. Of interest, general anesthesia with endotracheal intubation in non-fasted children may have greater risk of pulmonary aspiration than ED PSA.

Case 2

A 5-year-old girl has a closed *distal radius fracture*, dorsally angulated 30° but hinged at the cortex. She gets "car sick" and had multiple episodes of vomiting after an operation last year.

Issues: Pain management, history of motion sickness, and postanesthesia vomiting, and optimum technique for a painful but brief fracture reduction. Of note, in young children, some orthopedic surgeons do not reduce metaphyseal fractures "minimally displaced" in the primary plane of motion because they will remodel to normal over the coming months. Standardized determination of how much

displacement will successfully remodel remains to be developed.

1. *Pain relief*: please see Case 1. Splinting and oral oxycodone likely are sufficient.
2. *PSA technique options*: Since this fracture reduction will take "one brief but painful push," effective local anesthesia or brief deep sedation with rapid recovery is desirable.
   (a) *Nitrous oxide* (*50–70%*) *plus fracture hematoma lidocaine block*: This fracture may not have a significant hematoma, thus reducing the effectiveness of a hematoma block. Combining 70% N_2O with oxycodone, 0.2 mg/kg orally without the hematoma block, may provide sufficient analgesia and partial amnesia for remaining pain. N_2O should be administered for at least 2 min prior to reduction to maximize the gas's effects. Balancing potentially incomplete PSA against the benefits of not needing vascular access and rapid recovery should be discussed with the parents. A downside to this technique is the 25% likelihood of vomiting when N_2O is coadministered with an opioid. Coadministration of oral midazolam with N_2O (without oxycodone) reduces vomiting but prolongs recovery. It is unknown if oral ondansetron significantly reduces vomiting with N_2O and oxycodone.
   (b) *Ketamine with or without Midazolam intravenously*: Since this fracture reduction will likely be very brief, experienced providers may consider *rapid administration* of *ketamine 0.5–0.75 mg/kg* (pushed over 3–5 s) to induce about 5 min of deep sedation, with additional ketamine given if necessary. The performer of the fracture reduction should be ready as the ketamine is infused. With the single small rapid dose, deep sedation will occur within 1 min and recovery to being drowsy but responsive to verbal stimulation will occur by 10–15 min, often as casting is completed. Alternatively, administered over 30–60 s, ketamine 1.25 mg/kg provides deep sedation for 10–15 min with recovery by about 30 min or ketamine 2 mg/kg provides deep sedation for 15 min with recovery by an hour. *Vomiting* frequency after small dose ketamine is unknown. See Case 1 for additional information.

   Intramuscular ketamine 4 mg/kg provides effective PSA but recovery is significantly longer than with intravenous ketamine. See Case 1 for additional information.
   (c) *Fentanyl with Propofol or Midazolam* intravenously provides effective PSA for fracture reduction but with more respiratory depression than ketamine techniques (desaturation to less than 90% in approximately 25%-FM vs. 20%-FP vs. 5%-KM). Since respiratory depression/apnea occur frequently, providers should be experienced with this technique and well prepared to provide ventilatory support. Vomiting is less frequent with propofol than ketamine-based techniques. Recovery is faster with propofol/fentanyl than with ketamine/midazolam-based PSA (23 vs. 33 min in one study), especially if repeated doses are needed. Recovery is described as more pleasant after propofol sedation compared to ketamine. Time to discharge after fentanyl/midazolam is similar to that of ketamine/midazolam.

Case 3

A 3-year-old boy has blistering *hot water burns* to his right face and much of his anterior chest and abdomen, sustained when he pulled a pot with boiled water off the stove top. He was transported to the ED by EMS who was unable to insert an IV catheter, in part due to the child's obesity (weight 23 kg). The child has a history of mild asthma without hospitalization, controlled with albuterol MDI

as needed. He has had a runny nose and cough without fever for 1–2 days; his usual snoring while sleeping has worsened with the URI. The child is crying loudly and coughing as he is placed in a treatment room. Good air exchange with expiratory wheezes bilaterally is noted on auscultation.

Issues: rapid pain relief, difficult vascular access, obesity, history of snoring, asthma with current wheezing, and upper respiratory infection.

1. Rapid pain relief options:
   (a) *Fentanyl intranasally* 1.5–2 μg/kg, achieves significant pain relief within 5–10 min. See Case 1 for additional information. Base dose on estimated lean body weight (~15 kg for 3 year old); initial 2 μg/kg dose for this child is 30 μg or 0.6 mL. Divide the 0.6 mL total dose into four sprays of ~0.15 mL/nostril. The impact of an acute URI upon transmucosal absorption is unclear.
   (b) *Nitrous oxide 50–70%* will provide rapid pain relief, but its analgesic effect is lost within minutes when the gas is stopped. N_2O can be administered while IV catheter insertion is attempted. Use of a continuous circuit or N_2O delivery system easily activated by a young child is necessary.
   (c) *Oxycodone orally*, or other potent oral analgesic, will provide pain relief but onset is 20–40 min. For this young patient with a very painful injury, an initial oxycodone dose of 0.3 mg/kg is given orally, based on estimated lean body weight of 15 kg it is 4–4.5 mg. This dose may result in mild sedation as pain relief is achieved. See Case #1 for additional information.
   (d) *Opioids intravenously* titrated to effect will provide the greatest pain relief, if vascular access can be achieved. Fentanyl 1–2 μg/kg will provide analgesia within 1–2 min, lasting 30–60 min, whereas morphine 0.1 mg/kg will provide initial analgesia within 5–10 min with peak effect at 10–20 min and lasting 2–3 h.
   (e) *Intramuscular ketamine* 4 mg/kg provides rapid and marked pain relief and PSA without vascular access. Please see Case 1(b) for further information. If providers are available to monitor the patient and begin debridement, this may be a reasonable option. The greatest risk with this technique is that emergent vascular access to manage a life-threatening adverse event such as laryngospasm would be difficult, but an intraosseous needle could be placed, if necessary. IV catheter insertion for ongoing care can be attempted concurrently with the burn debridement.
2. *Difficult vascular access*: *Buffered lidocaine injected subcutaneously* with a 30 gauge needle provides nearly painless rapid local anesthesia for IV insertion. Use of this or other local anesthetic technique in this obese child will be especially important because multiple attempts likely will be needed. Because of the prolonged onset, topical anesthetic creams are not an optimum choice for local anesthesia. If available, *N_2O 50–70%* will reduce IV insertion-related distress as well as provide systemic analgesia as described in (b).
3. *Obesity, snoring*: As noted earlier, determine medication doses upon estimated lean body weight. Since fat is less perfused than brain and muscle, doses based upon total weight will result in higher initial plasma and brain concentrations and greater risk of adverse effects, and prolonged recovery. Obesity also reduces lung functional residual capacity, increasing his risk of hypoxia with respiratory depression, and increases likelihood of upper airway obstruction as indicated by his history of snoring. Use of supplemental oxygen during sedation of this patient will provide a greater margin of safety by prolonging the time to hypoxia if decreased ventilation occurs. Monitoring with end-tidal capnography, in addition to

pulse oximetry, will facilitate early detection of ventilatory insufficiency and allow supportive interventions before adverse consequences occur.

4. *History of asthma, currently wheezing, acute URI*: If the patient's wheezing clears readily with a single albuterol nebulization treatment, the increased risk of sedation-related adverse respiratory events likely is low, but providers should be prepared to administer additional asthma care if needed. The acute URI may increase the risk of laryngospasm, especially if the patient is febrile. It is unclear whether administration of a drying agent such as glycopyrrolate or atropine reduces this risk.

PSA Technique Options

(a) *Ketamine with or without Midazolam*: If vascular access is successful, the intravenous route is preferred as it allows titration to effect and use of the smallest effective dose, with repeat small doses as needed, thus decreasing length of recovery. Please see Case 1 for further information on ketamine dosing. It is likely this patient will need multiple subsequent painful burn debridements. Therefore, effective analgesia and amnesia for this initial burn care are especially important to establish the patient's future expectations. A sedating dose of midazolam, 0.1 mg/kg, prior to ketamine infusion, may increase the probability of complete procedural amnesia. A potential additional benefit for this patient is ketamine-induced reduction of central sensitization and windup from continued burn pain. While the risk of laryngospasm associated with ketamine is quite low, the presence of an active URI may increase this risk and the sedation providers should be prepared to manage this potentially life-threatening adverse event.

Intramuscular ketamine 4 mg/kg: Please see Case 1 for additional information.

(b) *Fentanyl + Midazolam or Propofol*: provides effective PSA but requires vascular access. Please see Case 2 for additional information.

(c) *Nitrous oxide 50–70%* is unlikely to provide sufficient PSA for vigorous burn debridement in this young child unless it is coadministered with a potent systemic analgesic such as fentanyl or ketamine. These combinations can readily induce deep sedation and general anesthesia and should be considered only by providers experienced in such techniques.

Case 4

A 2 year-old boy has a *complex forehead laceration* that requires suturing. Topical anesthetic gel was applied in triage. Despite best efforts to calm him as he sits in his mother's lap, he continues to cry and vigorously resists exam. His mother predicts he will not calm and indicates this is typical behavior during interactions with healthcare providers.

Issues: The laceration repair requires the patient's forehead to be still, physical restraint will likely reinforce similar behavior during future health care; there are other ED patients waiting more than 4 h to be seen.

PSA Options

(a) *Nitrous oxide 50–70%* provides effective calming for laceration repair in young children. A continuous circuit or other N_2O delivery system with a standard mask that covers the patient's mouth and nose and is designed for use by children is necessary for effective PSA with N_2O. Dental type nose masks are less effective since they allow mouth breathing that bypasses the N_2O. If the laceration is on the chin or in an area covered by the standard mask, a neonatal size mask may be used as a nose-mask and the child's mouth gently

held closed. If the mother is amenable, this technique can be enhanced by administering the N_2O and suturing as the child sits in her lap with his head rested on her chest and her singing favorite songs or telling stories for distraction. A helper will need to help steady the child's head and gently hold the mask in place over the patient's mouth and nose. All must be vigilant for vomiting, often forewarned by abdominal or chest heaving. The N_2O should be administered for about 2 min before attempting to provide additional anesthesia (buffered lidocaine injected with a half-inch 30 gauge needle recommended) or suturing.

(b) *Midazolam intranasally* 0.2–0.4 mg/kg administered with atomizer to spray small volumes of concentrated intravenous solution (5 mg/mL) to improve absorption. Suggested dose for this 12 kg child is 5 mg or 1 mL. Divide the 1 mL total dose into four sprays of ~0.25 mL; alternate nostrils, allow about a minute between repeat sprays into a given nostril. Use of small volumes improves efficacy by reducing drainage of drug into posterior pharynx from which it is less well absorbed and causes an unpleasant taste. Onset of sedation occurs by 3–5 min with duration of 20–40 min. As with other routes of midazolam administration, some children become dysphoric instead of sedated. When administered with an atomizer, intranasal midazolam is well tolerated and achieves anxiolysis with mild sedation. If the intravenous solution is dripped into the nares without atomization, most children complain of a burning sensation.

(c) *Ketamine intramuscularly* 2–3 mg/kg provides effective PSA for suturing when local anesthesia is also used. Minor restraint may be needed in a few children with this dose. Onset of sedation usually occurs by 5 min and recovery by 60–80 min.

(d) *Propofol, Ketamine, or Fentanyl/Midazolam intravenously*: titration of any of these techniques will provide maximum effectiveness but intravenous access is required. Placement of an IV catheter in this resistant child certainly will require physical restraint unless it is inserted after sedation with N_2O, intranasal midazolam, or IM ketamine. Such strategy might be logical for a very complex laceration repair expected to last more than 20–30 min or involve a critical step that requires the patient to be motionless, such as approximating a lacerated eyelid margin.

Case 5

An otherwise healthy febrile 10-month-old infant needs *incision and drainage of a large buttock abscess*.

PSA Options

1. Ketamine IV or IM: see Case 2 for additional information.
2. Fentanyl + Propofol or Midazolam: see Case 2 for additional information.
3. Nitrous oxide + Oxycodone can provide acceptable PSA if effective local anesthesia of the abscess can be achieved. Field blocks with buffered lidocaine are variably effective for smaller abscesses but usually unsuccessful for large abscesses. For larger and deeper abscesses, the author has occasional success by partially draining the abscess through a small (~1 cm) incision through skin well-anesthetized with subcutaneous lidocaine. The abscess cavity then is gently refilled with the topical anesthetic solution commonly used for anesthetizing lacerations (4% Lidocaine, 1:100,000 Epinephrine, and 0.5% Tetracaine (L.E.T.)). After 30 min, the entire abscess cavity often is well-anesthetized and the patient tolerates widening the incision and debridement of the cavity under N_2O sedation.

Case 6

You are asked to provide sedation for *incision and drainage of a peri-tonsillar abscess* in a very anxious 5-year-old boy who vigorously resists oropharyngeal exams. He has had a runny nose and cough with low grade fever for 2–3 days.

Issues: Mild to light moderate PSA can safely be administered for I&D of peritonsillar abscesses in older children and teens who will cooperate with the procedure in the Emergency Department. However, this child will require deep sedation to overcome his resistance. Deep sedation by any technique carries increased risk of pulmonary aspiration due to variable blunting of protective airway reflexes. This patient will have blood and pus draining upon his larynx during the procedure. This patient should be considered for abscess drainage in the O.R. under general anesthesia, likely with endotracheal intubation.

For light PSA for peritonsilar abscess I&D in cooperative children, 30–45 min prior to the procedure we administer morphine for baseline pain management and glycopyrrolate to dry secretions. Five to ten minutes prior to the procedure, we administer 2 mg of midazolam for anxiolysis. If the patient has difficulty tolerating the mucosal injection of buffered lidocaine with epinephrine at the site of the abscess, we may infuse 0.1–0.2 mg/kg of ketamine immediately prior to the surgeon's incision, i.e., a small dose. The patient is able to follow commands but appears a bit dazed after the ketamine and usually is better able to tolerate the procedural pain. Laryngospasm has been found to occur more frequently during endoscopy with ketamine sedation, presumably due to direct stimulation of the larynx. Whether laryngospasm risk correlates directly with the dose of ketamine is unclear. Likewise, it is unclear whether risk of laryngospasm is increased with laryngeal stimulation by drainage from a peritonsilar abscess. Using this approach, none of our patients have developed laryngospasm during peritonsilar I&D in our ED.

Case 7

A 15-month-old boy has fallen through stair railings an hour ago and has a large hematoma on his left parietal area. He is irritable and restless. An emergent head CT scan to evaluate for intracranial injury has been ordered. The CT tech calls to state they cannot get the patient to lay still for the brief period of the scan and asks that the patient be sedated.

Issues: Need for emergent CT scan that requires motionless patient for about 1 min to conduct scan, potentially increased intracranial pressure from hemorrhage.

PSA Options

1. Pentobarbital intravenously will sedate patient but a full dose may cause mild reduction in blood pressure which impacts brain perfusion. The prolonged recovery from pentobarbital makes monitoring patient for neurologic deterioration difficult and may complicate plans for general anesthesia if emergent craniotomy is needed.
2. Ketamine intravenously 0.25–0.5 mg/kg, pushed rapidly, will provide brief sedation. Some restraint may be necessary. Blood pressure likely will be maintained and brief increase in intracranial pressure probably is not critical.
3. Propofol intravenously provides sedation but brief hypotension and respiratory depression may rapidly worsen patient condition.
4. Etomidate intravenously will provide sedation and recovery within 5–10 min with less risk of hypotension. Myoclonic jerks during induction of sedation tend to be brief but may interfere with scanning.
5. Midazolam intravenously may be insufficient for sedation.
6. Fentanyl intravenously for pain may be sufficient to coax patient to be still for the brief period, as needed.

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Sedation of Pediatric Patients for Dental Procedures

16

Stephen Wilson

The challenges of sedating a child for dental procedures are multifactorial [1]: The patient's age, health, temperament and emotional status, parental concerns, clinician philosophy on patient management, extent and quality of clinician training and experiences with sedation, state dental board regulation of sedation, issues of third party coverage or parental reimbursement, knowledge of and adherence by clinicians to sedation guidelines, facility preparedness, and support staff experiences are but a few of many important considerations. Equally important and challenging are the extent of the dental disease and the inherent requisites of those dental procedures which require complete patient cooperation, good manual dexterity, and dental materials whose outcomes are technically sensitive to and dependent on local factors in the operative field (e.g., salivary contamination). Probably the most disconcerting issue is that dental disease, more specifically dental caries or cavities, is the single most common chronic disease of childhood and it is preventable [2].

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Extent and Treatment of Dental Caries

Dental caries is the result of a process involving a bacterial infection wherein the metabolic, acidic by-products of certain bacteria over time slowly dissolve the mineralized portion of the enamel and dentin. The bacterial infection is usually transmitted by the mother, father, or others to the infant and bacteria may begin colonization as primary teeth begin erupting [3, 4]. Possible consequences of the destruction of enamel and dentin are pain and swelling due to pulpal involvement. A dental lesion or cavity may be isolated to a small portion of one tooth or affect all erupted teeth in an individual (see Fig. 16.1). Dental caries affecting the primary dentition may often continue with the same degree and severity when the permanent dentition erupts.

Definitive treatment of dental caries depends on the extent of destruction of the crown of a tooth. Small lesions can often be treated with tooth colored composite materials. Dental treatment may require amalgam restorations or crowns as the carious lesions increase in size and involve more of the crown structure both in depth and laterality. Sometimes the extent of caries is sufficient to involve the pulp chamber that houses the nerve and blood supply to the tooth resulting in the need for pulpotomies, root canal therapy, or extraction.

K.P. Mason (ed.), *Pediatric Sedation Outside of the Operating Room: A Multispecialty International Collaboration*, DOI 10.1007/978-0-387-09714-5_16,

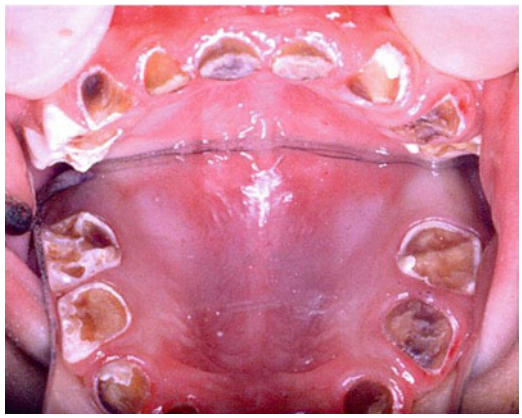

Fig. 16.1 Extensive dental caries

Dental treatment that enters into the dentinal aspect of the tooth usually requires local anesthetics for pain control associated with tooth preparation (i.e., instrumentation) or tooth conditioning (e.g., etching and bonding). Administration of local anesthetics involves needles and syringes which in and of themselves may cause patient anxiety and discomfort. Nerve blocks and infiltration with local anesthetics may not always result in profound anesthesia especially when the extent of caries has impacted the nerve chamber of the tooth or anesthesia administration (i.e., technique and/or amount) is inadequate. Simple classical conditioning that involves the pairing of dental instrumentation and pain including transmitted sounds and other sensations often result in patient discomfort, anxiety, and fear. Children, especially preschoolers, are particularly susceptible to such conditioning and may have limited psychological, emotional, and social resources to cope with its effects. Pharmacological management of the patient's behaviors during dental treatment may then become necessary.

The number of children who require sedation for dental treatment is unknown. One can estimate, based on information in a recent report [5], that pediatric dentists who use sedative agents other than nitrous oxide alone may sedate at least 300,000 children per year. This rate apparently has been slowly increasing over a 15 year period. In reality this is probably a significant underestimate of children who are sedated as the report involved a sample survey of pediatric dentists focusing primarily on orally administered sedation; and there are significantly fewer pediatric dentists in the country compared to the number of general practitioners who may also be administering sedatives to children. Furthermore, another survey report involving approximately the same magnitude of respondents as the previous study [5] indicated that the majority of pediatric dentists use nitrous oxide inhalation sedation on a routine basis [6].

Guidelines, Training, and Protocols

In 2007, the American Dental Association (ADA) published Guidelines for Teaching Pain Control and Sedation to Dentists and Dental Students along with a separate set of Guidelines for the Use of Sedation and General Anesthesia by Dentists [7, 8]. The ADA guidelines for Teaching Pain Control and Sedation to Dentists and Dental Students encourage psychological and pharmacological modalities [8]. Local anesthesia is stressed as the foundation of dental analgesia. The administration of local anesthesia, mild and moderate sedation are considered as skills which should be acquired in predoctoral or continuing education programs.

The curriculum for minimal sedation, a 16 h minimum course, should include nitrous oxide and enteral techniques. Intravenous (IV) and intramuscular techniques, in addition to the enteral and inhalation component, are taught with the moderate sedation curriculum. The Moderate Enteral Sedation Course is a minimum of 24 h didactics with ten adult cases (includes a mandatory three live adult cases). This course is not intended for the sedation of anyone under the age of 12. The Moderate Parenteral Sedation Course is a minimum of 60 h didactics and requires the management of a minimum of 20 patients via parenteral route of administration. This also is not directed for the sedation of patients <12 years of age. The sedation of <12 years of age requires additional supervised clinical experience and should follow the American Academy of Pediatrics/American Academy of Pediatric Dentists Guidelines for Monitoring

and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures [7, 9]. The administration of deep sedation and/or general anesthesia (GA) requires separate, directed education as approved by the ADA Commission on Dental Accreditation as well as current basic life support (BLS) and Advanced Cardiac Life Support (ACLS). The accompanying clinical staff(s) of the dentist(s) who provide deep sedation and/or GA all require current BLS certification [7]. The dentist providing the deep sedation or GA is permitted to perform the dental procedures as long as there are 2 BLS trained individuals present-one of which is designated to monitor the patient. All deep sedation or general anesthetics require a minimum of three individuals, including the dentist providing the sedation/anesthetic [7]. All deep sedation/GA requires IV access prior to initiating the sedation with the exception of brief procedures or the poorly cooperative child. In the latter case, the IV may be initiated after deep sedation/GA is initiated [7].

Many state dental boards issue permits that are necessary before a dentist can perform sedation during dental procedures. The training requisite for permits varies according to individual state board rules and regulations and the permitting process often may involve a system that is dependent on practitioner training and route of administration of the sedative. For example, a practitioner may be issued a permit limiting his/her sedations to oral administration only. A practitioner who is issued a parenteral IV permit can use any route of administration but not progress to a depth of GA. Only an individual who has a GA permit can administer any agent via any route of administration. These sedation providers are usually dental anesthesiologists or oral and maxillofacial surgeons.

The breadth and status of teaching received by dental students about pediatric sedation is minimal [10, 11]. Furthermore, it is likely that such experiences vary widely and are probably dependent primarily on faculty training, support services, and resources at each dental institution. It is no longer possible since the introduction of sedation permits, to sedate a patient without prior experience or training.

Specialty training in pediatric dentistry requires a minimum of 2 years and includes required didactic and clinical experiences in pharmacological management of children, according to the Commission on Dental Accreditation. The extent of those experiences in clinical context, quality, and quantity varies from program to program; and standardization of experiences among the 70 plus advanced training programs is unregulated and minimal. The overwhelming majority of programs primarily teach the use of the oral route of sedation. Rarely, IV sedation is taught and if so, a dental anesthesiologist or oral and maxillofacial surgeon provides that aspect of care.

In the private practice setting of pediatric dentistry, typically a single dentist or small group utilizes an office remote from a hospital or surgical center. Local resources of dental/medical anesthesiologists or other personnel trained in IV sedation are rare. The practitioner is left with little option but to provide minimal or moderate depths of sedation via the oral route, consistent with his/her training.

Five years ago, directors of pediatric dentistry training programs indicated that as compared to a decade prior, there was an increase in the volume of sedations as well as more didactic hours devoted to sedation, and the management of sedation-related emergencies [12]. More recently, the directors of these programs have the impression that there is a greater emphasis on sedation, likely reflective of the current influence of state board regulations, professional societies, litigation, and in particular, guidelines. Similar tendencies have been addressed in the medical community [13].

Sedation Protocols

Typically, a sedation appointment in a dental office or clinic involves multiple steps, all of which follow a protocol. The protocol encompasses all the steps: the informed consent process, preoperative instructions, presedation history and physical examination including airway assessment, weighing the child, administering the agent orally, waiting for a latency period wherein the effects of sedation become noticeable, placement

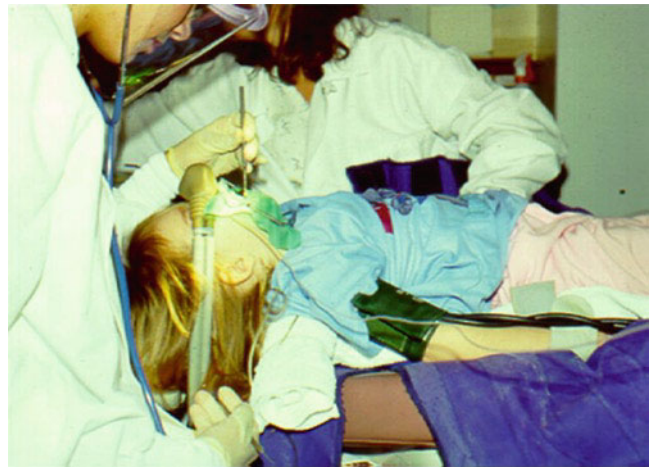

Fig. 16.2 Sedated dental patient with monitors

of the child in the dental chair and the nitrous oxide (N_2O) hood over the patient's nose, attaching monitors, proceeding with dental treatment, recovery, postoperative instructions, and discharge when appropriate criteria are attained (Fig. 16.2).

Sedative protocols used by pediatric dentists can be generally characterized as follows. The children selected for sedation are usually healthy (ASA I). Children who have medical conditions whose risk is more moderate to severe (greater than ASA II) are very likely to be sedated only in hospital-based settings with training programs. Most children are preschoolers although significant numbers of children are anxious and require sedation. Sedatives are administered almost exclusively via the oral route consistent with the predominant type of training currently occurring in programs [12], and the behavior and physiology are recorded while the child receives routine restorative care [14–27]. Usually, the behavior and physiology are documented on a time-based record by a dental assistant who performs interruptible tasks while working with the dentist. A standardized sedation recording sheet has been developed by the American Academy of Pediatric Dentistry, Committee on Sedation and Anesthesia that conforms to the protocol portion of the AAP-AAPD sedation guidelines (see Fig. 16.3).

Other incidental protocol events often include patient immobilization or stabilization (i.e., Papoose board®) [15, 20, 28–37]. Pediatric dentistry views the use of restraint not as punishment but as an intervention to improve the outcome or success of the sedation and procedure [38]. Pulse oximeters, blood pressure cuffs, and pretracheal or precordial stethoscopes are standard. Occasionally, side stream capnography is used but electrocardiography is rarely followed.

The choice of monitors is somewhat dependent on the behaviors exhibited by sedated children, the depth of sedation, and sedation guidelines. Behaviors and physiological parameters are fluid during the sedation, affected by the child's reaction to the stimulation, the timing of the more intense procedural stimulation, and the dentist's talents in calming or distracting the patient (rarely a part of study designs). For instance, heart rate typically increases most significantly and predictably during the injection of local anesthetics compared to other times of the procedure [14]. Generally, pediatric dentists target minimal or moderate sedation.

In most practices, a parent and child arrive at least 30 min prior to the sedation procedure for preoperative assessment, consent, and further review of the medical history. The time between oral administration of sedative(s) and initiation of treatment may vary from 10 min to an hour depending on the drug or drug combination used (e.g., midazolam vs. chloral hydrate [CH], respectively). The length of time involved with dental treatment range from 20 min to 2 h, according to the patient's dental needs. Recovery is usually done in the dental chair or a quiet room of the

dental office under direct parent and dental staff observation and monitoring. Discharge is consistent with the guidelines of the American Academy of Pediatrics and American Academy of Pediatric Dentistry [39].

Most older children can successfully cope with the experience of sitting cooperatively for routine dental procedures (including injections) and those who cannot tend to be preschoolers and toddlers. Age, cognitive and emotional development, maturational aspects of coping with challenging situations, and other characteristics of the child are well recognized as important discriminators for the clinician in recommending certain management techniques to the parent. Another characteristic that has shown promise in discriminating how children may react to novel clinical situations is temperament. The temperament of a child may influence the outcome of sedations and other techniques used by pediatric dentists in managing child patients [23, 40, 41]. Generally, the more approachable a

PATIENT SELECTION CRITERIA Date:_____

Patient: _____ ❑ M ❑ F Age:____yr____mo Weight:_____kg Physician: _____

Indication for sedation:
- ❑ Fearful/anxious patient for whom basic behavior guidance techniques have not been successful
- ❑ Patient unable to cooperate due to lack of psychological or emotional maturity &/or mental, physical, or medical disability
- ❑ To protect patient's developing psyche
- ❑ To reduce patient's medical risk

Medical history / review of systems (ROS)	NONE	YES*	Describe positive findings: _____
Allergies &/or previous adverse drug reactions	❑	❑	_____
Current medications (including OTC)	❑	❑	_____
Relevant diseases, physical /neurologic impairment	❑	❑	_____
Previous sedation/general anesthetics	❑	❑	_____
Snoring, obstructive sleep apnea, mouthbreathing	❑	❑	_____
Other significant findings (eg, family history)	❑	❑	_____

Airway Assessment	NO	YES*
Obesity	❑	❑
Limited neck mobility	❑	❑
Micro/ retrognathia	❑	❑
Macroglossia	❑	❑
Tonsillar obstruction (___%)	❑	❑
Limited oral opening	❑	❑

ASA classification: ❑ I ❑ II ❑ III * ❑ IV* ❑ E *Medical consultation indicated? ❑ NO ❑ YES Date requested: _____

Comments: _____

Is this patient a candidate for in-office sedation? ❑ YES ❑ NO Doctor's signature: _____ Date:_____

PLAN

	Name/relation to patient	Initials	Date	By
Informed consent obtained from	_____	_____	_____	_____
Pre-op instructions reviewed with	_____	_____	_____	_____
Post-op precautions reviewed with	_____	_____	_____	_____

ASSESSMENT ON DAY OF SEDATION Date _____

Accompanied by: _____ Relationship(s) to patient: _____

Medical Hx & ROS update	NO	YES
Change in medical hx /ROS	❑	❑
Change in medications	❑	❑
Recent respiratory illness	❑	❑
Weight:_____kg		

NPO status	
Clear liquids ____ hrs	
Foods ____ hrs	
Medications ____ hrs	

Airway assessment	NO	YES
Upper airway clear	❑	❑
Lungs clear	❑	❑
Tonsillar obstruction (____%)	❑	❑

Check list
❑ Appropriate transportation home
❑ Monitors functioning
❑ Emergency kit, suction, & O_2 available

Vital signs (If unable to obtain, check ❑ and document reason: _____)

Blood pressure: _____/_____mmHg Resp: _____/min Pulse: _____/min Temp: _____°F SpO_2_____%

Comments: _____

Presedation cooperation level: ❑ Unable/unwilling to cooperate ❑ Rarely follows requests ❑ Cooperates with prompting ❑ Cooperates freely

Behavioral interaction: ❑ Definitively shy and withdrawn ❑ Somewhat shy ❑ Approachable

Gurdian was provided an opportunity to ask questions, appeared to understand, and reaffirmed consent for sedation? ❑ YES ❑ NO

DRUG DOSAGE CALCULATIONS

Sedatives

Agent _____ Route _____ _____mg/kg X _____kg = _____ mg ÷ _____mg/mL = _____mL

Agent _____ Route _____ _____mg/kg X _____kg = _____ mg ÷ _____mg/mL = _____mL

Agent _____ Route _____ _____mg/kg X _____kg = _____ mg ÷ _____mg/mL = _____mL

Reversal agent

For narcotic: NALOXONE IV, IM, or subQ Dose: 0.01 mg/kg X _____kg = _____mg (May repeat after 2-3 minutes)

For benzodiazepine: FLUMAZENIL IV Dose: 0.01 mg/kg X _____kg = _____mg (NOT to exceed 0.2 mg/min & total dose of 1mg)

Local anesthetics (maximum dosage based on weight)

Lidocaine 2% (36 mg/1.8mL cartridge)	4.4 mg/kg X _____kg = _____ mg	(not to exceed 300 mg total dose)
Articaine 4% (72mg/1.8mL cartridge)	7 mg/kg X _____kg = _____ mg	(not to exceed 500 mg total dose)
Mepivicaine 3% (54 mg/1.8 mL cartridge)	4. 4 mg/kg X _____kg = _____ mg	(not to exceed 300 mg total dose)
Prilocaine 4% (72 mg/1.8mL cartridge)	6 mg/kg X _____kg = _____ mg	(not to exceed 400 mg total dose)
Bupivicaine 0.5% (9mg/1.8mL cartridge)	1. 3 mg/kg X _____kg = _____ mg	(not to exceed 500 mg total dose)

Fig. 16.3 (continued)

INTRAOPERATIVE MANAGEMENT & POST-OPERATIVE MONITORING EMS telephone number: _____ Monitors: ❑
Observation ❑ Pulse oximeter ❑ Precordial/pretracheal stethoscope ❑ Blood pressure cuff ❑ Capnograph ❑ EKG ❑ Thermometer
Protective stabilization/devices: ❑ Papoose ❑ Head positioner ❑ Manual hold ❑ Neck/shoulder roll ❑ Mouth prop ❑ Rubber dam ❑ _____

TIME	Baseline	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
Sedatives[1]																	
N_2O / O_2 (%)																	
Local[2] (mg)																	
O_2 sat																	
Pulse																	
BP																	
Resp																	
CO_2																	
Procedure[3]																	
Comments[4]																	
Sedation level*																	
Behavior*																	

1. Agent _____ Route _____ Dose _____ Time _____ Administered by _____
   Agent _____ Route _____ Dose _____ Time _____ Administered by _____
   Agent _____ Route _____ Dose _____ Time _____ Administered by _____
2. Local anesthetic agent _____
3. Record dental procedure start and completion times, transfer to recovery area, etc.
4. Enter letter on chart and corresponding comments (eg, complications/side effects, airway intervention, reversal agent, analgesic) below
   A._____ C. _____
   B._____ D. _____

Sedation level*
- None (typical response/cooperation for this patient)
- Mild (anxiolysis)
- Moderate (purposeful response to verbal commands + light tactile sensation)
- Deep (purposeful response after repeated verbal or painful stimulation)
- General Anesthesia (not arousable)

Behavior/responsiveness to treatment*
- Excellent: quiet and cooperative
- Good: mild objections &/or whimpering but treatment not interrupted
- Fair: crying with minimal disruption to treatment
- Poor: struggling that interfered with operative procedures
- Prohibitive: active resistance and crying; treatment cannot be rendered

Overall effectiveness: ❑ Ineffective ❑ Effective ❑ Very effective ❑ Overly sedated
Additional comments/treatment accomplished: _____

DISCHARGE

Criteria for discharge
- ❑ Cardiovascular function is satisfactory and stable.
- ❑ Airway patency is satisfactory and stable.
- ❑ Patient is easily arousable.
- ❑ Responsiveness is at or very near presedation level (especially if very young or special needs child incapable of the usually expected responses).
- ❑ Protective reflexes are intact.
- ❑ Patient can talk (return to presedation level).
- ❑ Patient can sit up unaided (return to presedation level).
- ❑ State of hydration is adequate

Discharge vital signs
Pulse: _____/min
SpO_2: _____%
BP: ____/_____mmHg
Resp: _____/min
Temp: _____°F

Discharge process
❑ Post-operative instructions reviewed with _____ by _____
❑ Transportation ❑ Airway protection/observation ❑ Activity ❑ Diet ❑ Nausea/vomiting ❑ Fever ❑ Rx_____
❑ Anesthetized tissues ❑ Dental treatment rendered ❑ Pain ❑ Bleeding ❑ _____ ❑ Emergency contact
❑ Next appointment on: _____ for:_____

I have received and understand these discharge instructions. The patient is discharged into my care at _____❑ AM ❑ PM

Signature: _____ Relationship: _____ After hours phone number: _____

Operator signature:_____ Chairside assistant: _____ Monitoring personnel signature: _____

POST OP CALL Date: _____ Time: _____ By: _____ Spoke to: _____ Comments: _____

Fig. 16.3 Sedation record consistent with American Academy of Pediatrics and American Academy of Pediatric Dentistry guidelines

child, the more likely the clinician can effectively interact and deliver care.

The oral route of administration remains the most popular route used by pediatric (and general) dentists [5, 10–12, 42–45]. The most probable reason for this route of administration is historical and related to individual experience. The IV route of sedation is the most popular for oral surgeons, although their need to sedate preschoolers is probably much less than that of pediatric dentists. The advantages and disadvantages of the oral route of administration compared to other routes are widely appreciated and understood even by parents.

The submucosal route is another fairly popular route of administration used by many pediatric dentists [23, 46–49]. This route of administration may limit the range and number of sedative agents

that can be used (e.g., CH cannot be administered via this route), but affords a clinical onset time and sedative impact more closely resembling IV compared to the oral route in children. The clinical effects happen relatively rapidly because children usually have excellent blood supply in and around the maxillary vestibules. Caution is advised because inadvertent and rapid injection of sedatives directly into blood vessels or a venous plexus can result in a more profound effect than anticipated. The submucosal technique is relatively easy to perform, and similar to administering local anesthesia for dental procedures, hence its relative popularity among pediatric dentists.

Sedatives

Most of the studies reported in the literature involving pediatric dentists focus on drugs or drug combinations involving CH, meperidine, and midazolam used in conjunction with other agents such as hydroxyzine [12, 14–26, 29, 33, 34, 36, 37, 41, 46, 48–95]. Occasional reports involve other benzodiazepines [32, 34, 93, 96–98] but their widespread use is not common. Rarely and usually in collaboration with a dental or medical anesthesiologist, other drugs such as ketamine are used and compared to other drugs or combinations [56, 61, 84, 99–106]. Other studies involve the IV or intramuscular routes usually done by or in collaboration with oral and maxillofacial surgeons or dental anesthesiologists, for school-aged children [27, 36, 52, 56, 78, 107–114].

CH was once the most popular sedative agent in pediatric dentistry. It still remains very popular. Its dosage range when used in combination with hydroxyzine, a relatively popular regimen, is 30–50 mg/kg CH and 1–2 mg/kg of hydroxyzine. A truly effective regimen is CH, meperidine, and hydroxyzine. The dosage range in this combination varies from a "low" dose combination (15–30 mg/kg CH, 1–2 mg/kg each of meperidine and hydroxyzine) to a "high" dose combination wherein the CH is relatively high but the meperidine and hydroxyzine are low (50 mg/kg CH, 1 mg/kg meperidine, and 25 mg of hydroxyzine). There seems to be a slightly higher incidence of true desaturations and apnea episodes in the "high" compared to the "low" dose combination but further study is needed. Studies have shown this "triple combination" technique to be relatively effective and safe [21, 33, 51, 53, 54, 59]. Yet, some postoperative events may raise some concern, even if discharge criteria are met [22].

The concept behind this triple combination is that all three agents induce variable degrees of drowsiness in a dosage-dependent fashion. Meperidine also provides euphoria and analgesia, reducing the amount of local anesthetic needed. Hydroxyzine provides some protection against mucosal irritation and vomiting. The effective onset time is usually 45 min and provides procedural sedation for 60–90 min, sufficient time for significant restorative dentistry. Most patients meet discharge criteria within 30–60 min following the dental procedure [21, 33, 51, 53, 54, 59].

Midazolam in recent years has surpassed CH in popularity as the most often used sedative agent among pediatric dentists. It is most often administered orally, but the intranasal (IN) route is also used frequently [28, 67, 79, 88, 115–118]. One of the shortcomings of orally administered midazolam is its short working time that is limited to approximately 20 min of restorative care. Its advantage is that its onset of action when given by this route is 10 min or less. It is the sedative drug of choice for short restorative or extraction cases for children who require sedation. Midazolam frequently is combined with other sedatives and analgesics which include meperidine or hydroxyzine. One of the primary purposes of combining these agents is to increase the restorative working time. The dose of orally administered midazolam when used alone varies from 0.3 to 1.0 mg/kg. When combined with other agents, the dose usually decreases to 0.3–0.5 mg/kg. Likewise, in combination therapy the dose of meperidine is reduced from 2 to 1 mg/kg. The oral dosages of drugs, patient findings and characteristics, and concerns of these sedative agents are shown in Table 16.1. Drugs such as etomidate are not utilized in the private practice community.

Table 16.1 Most commonly used sedative agents in pediatric dentistry[a]

Drug	Dose	Characteristics	Warnings	Sedation considerations (timing)	Reversibility
Chloral hydrate	20–50 mg/kg, max: 1 g	Oily Not-palatable Irritability Sleep/drowsiness	Airway blockage Mucosal irritant Laryngospasms Respiratory depressant Cardiac arrhythmias	Onset: 30–45 min Separation time: 45 min Work: 1–1.5 h[b]	No
Meperidine	1–2 mg/kg, max: 50 mg	Clear Nonpalatable Analgesia Euphoria Dysphoria	Respiratory depression Hypotension	Onset: 30 min Separation time: 30 min Work: 1 h[b]	Yes (narcan)
Midazolam	0.3–1.0 mg/kg, max: 15 mg (young child) 20 mg (older child)	Clear Nonpalatable Relaxation Anterograde amnesia	Angry child syndrome Paradoxical reduction Respiratory depression Loss of head righting reflex	Onset: 10 min Separation time: 10 min Work: 20 min[b]	Yes (flumazenil)

[a] This table reflects common dosing, warnings, and sedation considerations but must be interpreted and applied with caution. The table reflects the views of the author

[b] Work: the procedure duration usually tolerated following sedative effect

A recent paper reviewed the efficacy and adverse event profile of midazolam administered via different routes both alone and in combination with narcotics, also administered via different routes [119]. All patients received local anesthesia of lidocaine with epinephrine infiltrated into the gingiva. This was an important study because it evaluated the efficacy and safety of midazolam via the oral (PO) and the intranasal (IN) route and then examined the outcome when combined with oral transmucosal fentanyl citrate (OTFC) or IN sufentanil. There were four groups: PO Midazolam (1 mg/kg), IN midazolam (0.7 mg/kg), IN midazolam (0.5 mg/kg) + OTFC (10–15 μg/kg), IN midazolam (0.3 mg/kg) + IN sufentanil (1 μg/kg). IN midazolam had shortest time to onset (17 min) and similar efficacy to all the other groups. All groups were similarly efficacious (27% of sedations were graded as ineffective). The OTFC was the poorest performer with a 37 min time to onset and 39 min recovery (other groups 26.5–30 min). This study was important because it suggests that using midazolam via the IN route may be an efficacious method of delivery, eliminating need for parenteral administration and supplemental narcotics [119].

Nitrous oxide (N_2O) is the most frequently used anxiolytic and analgesic agent used in pediatric dentistry. Typically when used in dentistry, a nasal hood able to deliver nitrous oxide rests over the patient's nose (Fig. 16.2). Nitrous is delivered in an open system, thus entraining a significant amount of room air. In fact, adults and some children can decrease the proportion of nitrous oxide entering the lungs by consciously breathing through their mouth instead of through their nose or via other similar mechanisms (e.g., crying). At least one study using a dental delivery system has shown that the amount of N_2O entering into the lungs of patients is 30–50% less than the amount leaving the regulator portion of the dental N_2O delivery system [120]. Thus, if the dentist sets the N_2O flow to 50% at the regulator, only 25–35% of N_2O actually enters into the patient's lung.

N_2O is an excellent anxiolytic and behavior management agent when used in the range of 30–50%. It is also unique in that it provides mild analgesia at these concentrations, a mechanism which appears related to endogenous opioid systems [121]. For these reasons, N_2O is very frequently and effectively used with oral sedatives, primarily as the "titrating" agent for managing behavior. Another advantage for using a dental nitrous unit during sedation is that it provides supplemental oxygen. Nonetheless, caution must be used in these situations as N_2O in amounts often used in dentistry has been show to inhibit the swallowing reflex [122]. There are limited studies investigating the association of vomiting during exposure to N_2O for operative treatment in children and most suggest that vomiting is infrequent [123–125].

Morbidity and Mortality: Dental Sedation

The true number of adverse events that occur during sedation of children for dental treatment is unknown. Sometimes mild "adverse" events are reported in the literature but rarely, if ever, are of a nature requiring medical stabilization or admission to a hospital [15, 17, 55, 57, 58, 71, 74]. These types of adverse events may be temporary desaturations or apnea, usually associated with patient crying and behavioral posturing, vomiting, or paradoxical excitement. More significant adverse events such as laryngospasm, seizures, or coma are almost nonexistent in these types of studies. However, significant adverse events can and do happen and have been reported [126, 127].

The incidence of significant sedation-related adverse events in pediatric patients was reviewed and published in 2000. One-hundred and eighteen case reports were reviewed, for which 60 resulted in death or permanent neurologic injury. Twenty-nine of these critical events occurred in children sedated for dental procedures. The occurrence of death and permanent neurologic injury was associated with the administration of three or more sedatives. Nitrous oxide in combination with other sedatives was also associated with the negative outcome [95].

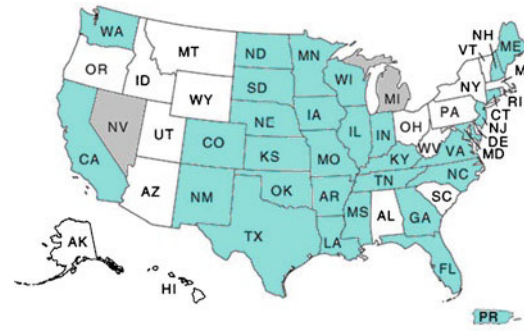

Fig. 16.4 States with general anesthesia coverage (*blue*) and those with negotiated regulatory coverage (*gray*)

Reimbursement for Dental Sedation and Anesthesia

Financial considerations of sedation for dental care are noteworthy. Most insurance plans do not cover the cost of sedation (including, nitrous oxide) or anesthesiology for dental purposes. Therefore, the parent is left with the financial decision of whether to pay for pharmacological management of his/her child in addressing delivery of restorative care or exodontia. However, 32 of the states have mandatory GA legislation that will cover some costs associated with the medical fees when a child receives dental care under GA (see Fig. 16.4). The fees for sedation procedures vary considerably among dentists but may range from $100 to several hundred dollars per sedation appointment. Some states have implemented legislation requiring some third party payors to reimburse fees for GA used in delivering dental restorative care. Nonetheless, often stipulations such as the patient's age or mental or emotional status may preclude some patients from receiving care.

Alternatives to Sedation

The alternatives to pharmacological interventions (i.e., sedation and GA) in managing fearful or uncooperative children during dental restorative or exodontia appointments may include, among others, psychological distraction techniques,

hypnosis, protective stabilization (i.e., restraints such as Papoose Boards®) or no treatment. No study has assessed the cumulative outcome of these nonpharmacological techniques of managing children's behavior and often the degree of success of these nonpharmacological techniques varies according to interpretation [38]. Anecdotally, there are many concurrent factors during operative procedures whose impact and interactions are acknowledged but unknown. These include the family's cultural background, child rearing techniques, the child's coping abilities in defending against potential physical and emotional trauma, and the quality of the work provided. Some dentists and parents perceive that if the needed treatment was completed it was a successful outcome. This perception may be out of necessity because of the influence primarily of financial factors associated with the compensation for the delivery of oral health care and traditional training experiences. Others refuse or reject these alternative means of treatment and elect not to seek care; however, the untreated dental disease does not regress and may progress to a localized abscessed condition or cellulitis. Cellulitis may be life threatening if it spreads to other organs (e.g., brain) and death may result.

Sedation Guidelines

Sedation guidelines for children have been followed by most pediatric dentists since they first were published in the United States in 1985 [128–130]. Coincidentally, the first guidelines of the American Academy of Pediatrics (AAP) were created in response to deaths in dental patients who received meperidine [130–132]. The most recent joint guidelines of the American Academy of Pediatrics and American Academy of Pediatric Dentistry emphasize, among other concepts, patient safety and rescue as well as practitioner education and training [39]. The impact of these latest guidelines (in terms of access to care, the number and types of sedations performed by pediatric dentists) remains to be seen. In that same vein, state dental boards regulate sedation performed by dentists. Most states require a licensed dentist to also have a special sedation permit. Different types of permits such as permits for enteral vs. parenteral routes of administration are issued to dental practitioners depending on several factors. Documentation of training, performance of sedation in the presence of a board consultant, and on-site inspection of offices often are required along with a fee prior to issuance of a given type of sedation permit to a licensed dentist.

Future of Sedation for Dental Procedures

In the future, sedation of children for dental procedures will continue to be influenced by societal demands, regulatory agencies, guidelines, financial implications, alternative options, and practitioner training as they are today. It has been promoted that in the future there are likely to be three groups of pediatric patients, classified by their response to the challenges of coping with dental procedures. The first group would be comprised of children who easily accept and adapt to dental procedures and thus would not require any pharmacological intervention. The second group may be slightly anxious and benefit from mild sedation or pharmacological adjuncts (e.g., nitrous oxide or a benzodiazepine). The last group would constitute those who exhibit highly anxious or fearful behaviors and cannot cope with the routine dental environment. This group would benefit from deep sedation or GA. The first two groups could easily be managed by pediatric dentists, even in today's settings and situations. The latter group is a challenge for many reasons, largely based on the current state of resources in all geographic regions of the country.

The progression and evolution of pediatric sedation for dentistry must involve a change in the entire training process. Oral routes of sedation for mild and moderate levels are no longer considered as efficacious as other routes. New sedatives, different delivery routes and evolving techniques can only, however, be applied with careful training (didactic and clinical). Changes in training, with pediatric-focused specialty training programs are the most critical first step. Conceptually, more intense, prolonged periods of training with partial

or full standardization of experiences across all training programs would be desirable. The extent and context of training would exceed that which currently occurs and must include well-defined and measurable competencies in emergency management, sedation protocol, patient assessment, and research. There are significant logistical hurdles to achieving this goal. Intense scrutiny innovative approaches, funding considerations, and administrative support are needed to achieve success. A simple example would be a method to train or retrain a cadre of faculty that can be disseminated to training programs in order to institute mechanisms for standardizing sedation protocols. Who will do the training? Are special "centers" required initially? How many and where? How long will it take? What are the funding mechanisms?

Focused communication, collaboration, exchange of innovative ideas, remodeling of current training programs or creation of novel training centers are desirable and necessary to initiate a comprehensive and humane plan for oral health care of children. Many regulatory issues will remain as obstacles to be addressed. The first steps in staging such an initiative require the broad-based recognition and acceptance of change in sedation training and philosophy. This step must subsequently be followed by the identification of dedicated individuals from different disciplines who collaboratively desire to improve the treatment options for pediatric dental care in the future.

Case Studies

Case 1

Patient is healthy (ASA I) and 3 years of age with no known allergies and parent seeks care for the child because of cavities noticed on the front teeth (chief complaint). Examination reveals 20 primary teeth, normal anatomy, and no soft tissue pathology. Of the 20 primary teeth, 13 involve frank carious lesions (4 maxillary incisors, 2 maxillary canines, and 7 molars). It is questionable as to whether the incisors can be saved. This presentation is referred to as early childhood caries which is currently defined by the American Academy of Pediatric Dentistry as "the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to caries), or tooth-filled surfaces in any primary tooth in a child 71 months of age or younger." The tonsils at the time occupied approximately 30% of the airway and the parent denied the child snored. The head and neck were symmetrical in shape and the jaws and occlusion were normal in development for a child of this age. The child weighed 16 kg.

When the child first saw the dentist, he demonstrated shy, withdrawn behaviors and sought comfort from his mother. Oral examination was difficult as the child was uncooperative, crying, and required the mother of the child to stabilize and hold the arms and legs in a knee-to-knee examination position with the dentist. Dental radiographs were not possible to attain due to behavior. A discussion of the child's oral condition and the scope of treatment modalities occurred with the mother. The mother does not have dental insurance that will cover sedation or GA and has to pay out of pocket should she elect to consent to sedation or GA. GA costs are too expensive for the family and she elects to pay for sedation using a payment plan. The child is scheduled for two sedation appointments; however, the mother is advised that depending on the child's response to the drugs selected, including local anesthesia, the number of appointments may be altered. The parent consents.

On the day of sedation, another oral examination including airway assessment is completed. The child has been NPO for 9 h. The

dentist decides, based on the number and type of procedures to be completed, to use a combination of sedatives that have been shown in the literature to be effective. CH (20 mg/kg), meperidine (2 mg/kg), and hydroxyzine (1 mg/kg) will be administered orally with a latency period of 45 min. Should the child spit out the medication or vomit before any dentistry is done, no further administration of sedative agents occurs. This combination of agents and doses are based on the expected amount of dentistry to be completed and the child's temperament and personality (i.e., clinically shy, uncooperative and difficult). Latency period refers to the time from administration of the oral agents to that when the child is taken to the dental operatory to begin delivery of care. Local anesthesia is limited to 64 mg (4 mg/kg) which is slightly less than 2 carpules. A carpule is the unit of local anesthesia that fits into a standard dental syringe which is typically 1.7 mL of 2% lidocaine with 1:100,000 epinephrine. This amount of local anesthetic can be distributed over two quadrants and includes an inferior alveolar block and buccal infiltration involving approximately half of the care needed to be finished.

At the end of the latency period, the child is placed supine in the dental chair. The child is awake, but drowsy and slightly less apprehensive of the doctor. An oxisensor of a pulse oximeter is attached to the second toe, a blood pressure cuff to the upper left extremity, a pretrachial stethoscope is placed over the upper airway above the manubrum, and plastic tubing from a capnography is readied should the child go into deeper levels of sedation. Nitrous oxide is initially administered using a nasal hood with the initial setting of 50% concentration; however, the child begins to fuss, struggle, and cry. The concentration of nitrous is raised to 70% (the maximum concentration attainable by a dental nitrous delivery system) and the hood held slightly above and over the nose and mouth of the patient. Within 5 min of distracting the child and administering the nitrous oxide, the child settles down and demonstrates slight ptosis of the eyelids. The nitrous concentration is immediately lowered to 50% and the hood placed lightly over the nose. This process of using the nitrous to calm the child is called "settling." (If settling does not work within 10 min of nitrous administration, either the nitrous is no longer used and the decision is made with the parent and his/her consent to either proceed using local anesthesia and a papoose board or reschedule the patient for another appointment during which a slightly different drug regimen is used or altering the dose of the current regimen. The child is kept in the dental clinic until they have recovered enough to meet discharge criteria.) The child is now comfortable and cooperative.

A small dollop of topical anesthetic is applied to the soft tissues where the injection will occur. The local anesthetic is slowly administered using an aspirating dental syringe and this elicits crying and new struggling on the part of the child. Once again, the "settling" procedure is done after the anesthetic has been administered. The child settles. A rubber dam is applied to prevent aerosol spray, tooth debris, and water from the dental handpiece from going into the child's airway. High speed suction to remove the debris and water is also done by the dental assistant. The child is reactive and has low intensity crying, minor movements, and no tears. Toward the end of the procedure the child becomes quiet and the eyes close. Besides the auscultation of the airway sounds, the plastic tubing from the capnography is taped under nostril orifice of the child and the excursions monitored by the dentist and assistant. The dentist asks the child if they are "doing OK" and the child responds with a slight nodding of the head to which the dentist replies that we are "almost done." The work is completed. Seven teeth are restored with the restorations involving stainless steel crowns and white composite restorations. The child is stimulated by the dentist lightly tapping the child on the shoulders and declaring that "we

are all finished." The child is slowly raised to a sitting position and reunited with the parent. The parent is informed of the procedures that were completed, how much remains, and the patient's responsiveness during the procedure. It turns out that this child exhibited "quiet" behaviors (no crying, but either eyes open or eyes temporarily closed) approximately 70% of the time with the remainder of the operative time involving crying and struggling behaviors. This is "typical" of this particular regimen and younger children. The child is kept until discharge criteria is met (usually this occurs within 30 min after the dental procedure is completed). Another sedation appointment is booked and the plans are to use the same drugs and dosages as this appointment.

Case 2

Patient is healthy (ASA I) and 2 years of age with no known allergies and parent seeks care for the child because of cavities noticed on the front teeth by the parent and the child is complaining of sensitivity to cold (chief complaint). Examination reveals 17 primary teeth, normal anatomy and no soft tissue pathology. Of the 17 primary teeth, the four maxillary incisors are grossly carious and a draining fistula is noted above the right central maxillary incisor. The indicated treatment is extraction of these four incisors due to nonrestorability and periapical abscess. The tonsils are approximately 60% of the airway and the parent indicated the child snored occasionally during sleep. The head and neck were symmetrical in shape and the jaws and occlusion were normal in development for a child of this age. The child weighed 14 kg. Vital signs are within normal limits. The patient has been NPO since 10 p.m. the previous evening.

The patient was approachable and interacted with the dentist but was age-specific hesitant and exhibited facial expressions suggestive of mild apprehension and anxiety for his age. He is classified temperamentally as "slow to warm up" and typical of a patient of his age. It was possible to obtain a maxillary dental radiograph confirming the abscess as well as caries encroaching on the pulp chamber of the remaining incisors. The sedation plan is to use midazolam (0.75 mg/kg) administered orally.

The midazolam is drawn up, flavored, and administered by cup. Due to the rapid onset and short duration of working time, it is planned to begin the procedure at 10 min after administration. The child is brought to the dental chair 10 min after drug administration and is placed on 50% nitrous oxide using a nasal hood. The patient is loosely wrapped in a papoose board (with parents consent gained previously along with that for the sedation). The patient is somewhat uncooperative initially but finally accepts the mask. A pulse oximeter and blood pressure cuff are applied with a precordial handy on the assistant tray.

A dentipatch (concentrated lidocaine topical on a tiny "band-aid") is placed in the maxillary vestibule overlying the four incisors which had been thoroughly dried with a 2×2 gauze. The patch is left in place for 10 min as is the nitrous oxide. Stories are told to distract the patient. The patch is removed. Next, a carpule (1.7 mL of 2% lidocaine with epinephrine 1:100,000) is slowly administered by way of a dental syringe. This causes some minor movement with vocalization, especially when the palatal tissues are anesthetized. The child is consoled and distracted. A period of 10 min passes during which the heart rate and oxygen saturation are monitored and recorded. The child's behavior is one of quietness but is beginning to cry intermittently; nonetheless, distraction techniques are effective.

The four maxillary incisors are extracted using a curette and forceps without incident. The heart rate rose slightly, the child was interactive and struggled mildly, but expressed little discomfort indicating that the local anesthetic was effective. Pressure and gel-foam were used to obtain hemostatis. The child is losing

tolerance for the procedure and is becoming more vocal with his crying and movement and expressing a desire to see his mother.

The mother is reunited with the child and postoperative instructions are given. The child begins to settle down initially. The parent and patient are kept in the dental room but now the child is becoming agitated, nonconsolable, and crying intensely. The child rips the oxisensor off the toe The child, although relaxed, tries to escape from the parent. The child is now exhibiting the "angry child syndrome" that is often seen (at 20% of the time) during dental procedures in which midazolam is used as the primary sedative agent. The parent had been forewarned of the possibility. A decision of whether to reverse the emotional condition with flumazenil is considered, but its shorter duration of action compared to the midazolam is a potential problem as explained to the parent. The patient is kept another 30 min and can now ambulate with assistance but continues to be disruptive and angry. After 15 more minutes, the child is discharged into the care of the two parents. The family is called 2 h later and the child has now settled down, is consuming clear liquids and soup.

Case 3

A 10-year-old female is referred to the office by a general practitioner who was unable to talk the child into receiving local anesthesia due to extreme apprehension and needle phobia for the extraction of a carious, nonrestorable first permanent molar and three other restorations. Patient is fearful and guarded but is complaining that the pain from the molar increases and ibuprofen is not helping anymore. A clinical examination is done with a great deal of tell-show-do, distraction, and coaxing necessary. The dentist and assistant attempted to behaviorally walk the child through intra-dental radiographs, but failed. Extra-oral radiographs are obtained with difficulty and confirm the molar is nonrestorable. Vital signs and an airway examination are completed. They are within normal limits. The patient has not eaten since 7 p.m. the previous night. She weighs 37 kg.

The dentist decides to use diazepam (7 mg) and meperidine (2 mg/kg, but limits the dose to 50 mg). The patient reluctantly drinks the flavored medications in a vehicle of ibuprofen (100 mg) elixir. The patient becomes more relaxed 30 min after drug administration but still guarded. At 45 min after drug administration, the patient is introduced to the nitrous oxide hood but refuses to accept it and becomes more anxious with inconsolable crying. Attempts are made to calm the patient with some success. Topical anesthesia administration is done but the patient limits mouth opening despite encouragement. A mouth prop is inserted and this agitates the patient. Although the usual distraction and "out of sight" passing of the syringe is done, the patient's eyes follows the hand exchanges between dental assistant and dentist. The patient begins to scream and makes concerted efforts to escape from the chair despite being incoordinated. The syringe is replaced on the dental tray and efforts are made to calm the patient again. The sequence of events is repeated but is not successful in overcoming the patient's will and lack of cooperation. The child is inconsolable and wants to go home. It is decided to cancel the session and perform the dentistry under GA in an outpatient care setting. The patient is duly monitored with a pulse oximeter until discharge criteria are met almost 1.5 h after the drug administration.

The parent's insurance does not cover sedation or GA for dental procedures. The parent wishes to wait and research possible financial resources. Two weeks pass and the patient returns to the office in chronic, moderate to severe pain, moderate trismus, and some localized swelling which is affecting daily home functions. The patient is referred to an oral surgeon who reluctantly accepts a payment plan with the parents and uses deep sedation to remove the offending molar. The patient never returns to the office for follow-up on the three remaining carious lesions.

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Pediatric Sedation: The European Experience and Approach

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Michael R. J. Sury and Piet L. J. M. Leroy

Introduction

Every system of health care is imperfect because it has limited resources and must cope with increasing demand. Europe has many independent countries and each health service has been influenced by historical, cultural, social, and economic factors. For the management of children having minor diagnostic and therapeutic procedures, there remains considerable variation in practice. Nevertheless, healthcare providers in Europe have been influenced by recommendations from within Europe and the United States (US), and this has led, and will continue to lead, to a general improvement in the quality of services available.

This chapter avoids reiteration of what is commonly known in the United States, and instead is intended to describe and contrast what is different or new in Europe. In doing so, we have drawn upon our personal knowledge, researched the European literature, and gathered some of our own data to describe what we believe to be the important and interesting European problems and perspectives with pediatric sedation.

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General Problems

Demand for Sedation and Anesthesia

In the last 15 years, the demand for procedures has increased and the availability of anesthesia services has decreased, if not in absolute terms, in proportion to the demand. Five services are prominent and each is discussed in detail. It is reasonable to state that, because of the characteristics of the procedures, each service requires a different sedation strategy and set of techniques. Nevertheless there are similarities in terms of the facilities they need. For specialists planning and negotiating the development of a new service, it may be helpful to consider what facilities are needed. A basic but invaluable list was created by a group of London hospitals who are trying to measure their progress in their compliance with the standards set out in the UK (United Kingdom) Children's National Service Framework (http://www.ich.ucl.ac.uk/cypph/cnsf_audit_tool.pdf). In a section on Pain, Symptom Relief, and Sedation there are six facilities:

- Analgesia
- Procedural sedation
- Rescue Anesthesia
- Behavioral management (play therapy)
- Long-term central venous access
- Symptom control

All of these will help minimize distress and a comprehensive service should have them. There is debate concerning the pros and cons

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of sedation verses anesthesia but the most important questions are about what happens when anesthesiologists are not available;

1. What drugs are safe enough for nonanesthesiologists to use?
2. What minimal competences and skills should nonanesthesiologists possess to ensure an optimal level of both safety and effectiveness?

Behavioral management is becoming an essential tool, [1, 2] and behavioral skills need to be embedded in training of everyone in the healthcare team– not just Play Specialists and Psychologists. Behavioral management skills help to reduce anxiety and the need for sedation drugs and their value should not be underestimated. Self hypnosis and other coping strategies are useful for cooperative children [3, 4]. Likewise, the early insertion of central intravenous lines avoids many painful venipunctures: interventional radiology services have radically reduced distress in children. There is a wide and strong belief that if children, especially those who need repeated procedures, undergo their first procedure without distress, subsequent procedures are more easily managed and suffering is reduced overall. There is little published evidence for this view.

There are major cultural aspects to the demand for and the practice of sedation. A survey of practice in the US and Europe highlighted major differences in the use of sedation and analgesia for oncology procedures [5] and although the replies may no longer apply, they could be taken as evidence of an acceptance by many children and parents in the US that sedation and analgesia were not necessary for bone marrow aspiration and lumbar puncture. Perhaps the survey was not truly representative, but there is other evidence of cultural behavior having an effect. In France, many painful procedures are undertaken with nitrous oxide alone [6, 7], and it is surprising that this practice has not transferred to other countries; probably it is not transferable because patients and parents expect and prefer anesthesia. Nitrous oxide is given without the need for special facilities or fasting, a clear advantage over anesthesia. In the Netherlands, a group of midwives have given birth to infants with major congenital defects. Nitrous oxide was blamed and is no longer available in that country for obstetric analgesia (it is still available for dental sedation). A working group on pediatric procedural sedation is trying to introduce nitrous oxide for procedural sedation but is facing strong opposition.

Also in France, parents are discouraged from remaining with their children during procedures or at induction of anesthesia. In other countries parents are encouraged to be present in many situations, even during resuscitation [8].

There are, within Europe, large differences in choice of sedation drugs. Chloral hydrate is the first-choice drug in the Netherlands for sedation in diagnostic imaging because it has a high safety profile and success rate. In France it has been banned because of suspicion of genetoxicity and carcinogenicity [9].

Physical restraint is a taboo subject. The literature suggests that the application of “straps” in precooperative small children was acceptable in some hospitals or situations in the US [10–12] but perhaps less so in the UK [13, 14]. There are specific guidelines in the UK for the appropriate use of restraint and which prevents the restraint of an uncooperative child without effective sedation of anesthetic drugs [15]. In Scotland it is illegal to use physical restraint and there are aspects of European Law of Human Rights that prevent restraint also. Several European authors have postulated that procedural restraint is contrary to the Human rights act and the United Nations Convention on The Rights of the Child [16, 17]. The European Association for Children in Hospital states in their charter that avoidance of restraint should be a fundamental part of comfort policy in sick children (http://www.each-for-sick-children.org). Nevertheless, restraint is still common practice within European pediatric medicine and it is our experience that in general, procedural comfort is not yet considered essential.

Anesthesia Services are Limited

The following discussion may apply throughout the developed world but is included here to help explain the practice of nonanesthesiologist led sedation. Anesthesia has been developed for

surgical operations and the development of services outside the operating theater has been slow. Several reasons may explain this. Anesthesia has been developed to provide surgeons with efficient operating lists. Pediatricians, in contrast, have not scheduled their cases in a similar fashion and have not always pressed their need for services. Consequently they have tried to manage on their own with the intention of giving themselves control and responsibility; this has had limited success. Anesthesiologists have been reluctant to help them because resources have not been vouched safe and facilities may not have the standards of operating theaters – at least that was a common perception. There was also a fear of working unsupported at a site remote from other anesthesia colleagues. Given these problems, pediatricians, had no choice but to cope with providing sedation on their own. Anesthesiologists who could help provided anesthesia considered perhaps as unnecessary, out of proportion, higher risk, or more expensive than sedation. Finally, there was an underlying view that once a service was given to pediatricians, it would lead to a considerable increase in demand that would not be possible to satisfy – it was a "bottomless pit." Eventually, with reports of unsafe or ineffective practice, anesthesia services outside theaters have flourished. Today, at least one third of all pediatric anesthetics are given outside surgical operating theaters. Nevertheless there are issues that slow the transition to ready access to good services. We outline them below.

Small hospitals continue to be attractive to the public, who believe that they provide a good service. These units are too small to provide tertiary (specialist) care and possibly unable to provide secondary care if it involves nonstandard techniques – in current health services, pediatric care is classified as nonstandard and requires special training. This varies between countries. A small unpublished survey last year showed that in Belgian regional hospitals, most MRI scans in children are done under modern general anesthesia while in the university units, old-fashioned sedation cocktails are still in use because of limited anesthesia resources. In the Netherlands the opposite is true.

Mortality studies of surgery and anesthesia in the UK and elsewhere have identified that the very young and the very old have a higher risk than others [18]. Consequently, this led to specialization and a withdrawal of services to children by anesthesiologists who thought their skills were not sufficient. Some hospitals withdrew pediatric surgery from their services – perversely some Emergency Departments continued to accept pediatric trauma and medical problems that may need anesthesia and intensive care. This remains a common scenario around Europe. Both national as well as European centralization of tertiary care is a problem. Fortunately, the links to larger centers are usually well established and transfer is not difficult although there will be an inevitable delay in treatment. To avoid the need for transfer, some hospitals have developed sedation protocols, mainly ketamine, to help children with minor injuries. A far reaching effect of specialization is the closure of small pediatric units and the expansion of others. This has lead to improvement of services because anesthesia services can be developed economically to deal with larger numbers of cases in dedicated sessions and facilities outside operating theaters.

The European Working Time Directive has limited the hours that doctors can work. It is a statute developed in the EEC to prevent excessive working hours and to encourage more equitable employment. For example, it may be fairer to employ two doctors to work 36 h per week rather than one for 72; night duty, even if the doctor is in-hospital and asleep, counts as work. This directive, however, is allegedly not applied uniformly across the continent, but in the UK it has severely limited training experience for trainees. Since August 2009, the limit has been set to 48 hours per week.

In 2003, a new UK consultant contract changed the behavior of many consultants. Before 2005, most consultants (nontrainees) worked sessions and provided services that were not fixed nor agreed by contract. Such an unclear system of employment was vulnerable to criticism of ineffective management and this persuaded the politicians to demand clear agreement and contracts. Now, work is fixed by contract. However, this does not seem to have increased patient throughput but it may have encouraged improvements in efficiency. Yet, part of the debate has been about

quality of services rather than quantity. A system of fee for session and, as in the US, fee for service, limits flexibility and prevents natural changes in service. If a pediatrician wants a sedation service, and asks for anesthesiologists to provide it, will he deliver anesthesia rather than sedation? Reimbursement based on service can have perverse outcomes, such as preventing the use of simple effective techniques in preference to financially advantageous anesthesia. Another problem relates to the case throughput. If payment is too low there is incentive for fast techniques that may not be safe or effective. Mindful of these problems, the payment by salary unrelated to number or complexity of cases, allows the practitioner to provide a service tuned to the needs to the patients.

In France, preoperative assessment by an anesthesiologist is compulsory, by law, at a minimum of 24 h before any routine procedure. This has restricted the involvement of anesthesia services in the delivery of sedation or minimal anesthesia for children and encouraged the use of nitrous oxide alone by nonanesthesiologists.

Nonanesthesia Practitioners

In the UK and much of Europe, anesthesia is a physician led service. In Scandinavian countries and the Netherlands, nurses are employed to assist physicians; they look after patients during surgery but they are supervised by physicians and not by surgeons. This system may develop in the UK but, because there is a surplus of trained anesthesiologists, it is not likely to grow significantly in the foreseeable future. In pediatric anesthesia, almost all anesthesia services throughout Europe are physician led.

Because of the scarcity of pediatric anesthesiologists, several professional groups have had to use drug techniques that have the potential to become accidental anesthesia. The dentists, emergency physicians, and intensivist have been prominent. Their *journey*, from inexperienced sedationist to practitioner with proven but limited anesthesia skills, has not reached its end. It is inevitable that they must continue in the venture to provide effective and safe services for their patients. Once rigorous competences, skills, and safety precautions have been fulfilled, nonanesthesiologists in Europe have been given access to potent sedatives (e.g., Propofol) [19, 20]. However, this is as controversial in Europe as it is in the US: [21].

Challenges and Setbacks

Safety issues, adherence to guidelines, and the training and skills of the sedation provider have been of recent concern in Europe. Three cases with disastrous outcomes have attracted widespread notoriety and press in Europe.

- A child's brain was damaged by 100% nitrous oxide given from an anesthetic machine that did not have a hypoxic mixture alarm. The practitioner was untrained in its use.
- A child died after being suffocated by a team trying to use a breathing system to deliver a nitrous oxide/oxygen mixture because they failed to turn the gas flow on. They were untrained.
- A combination of midazolam alfentanil and ketamine was given to sedate a boy for dental extractions. He became apneic soon after arrival in the recovery area and, neither the nurse nor the doctor reacted quickly enough to prevent permanent hypoxic brain damage [22].

Lack of sufficient training was the prominent issue with these cases and although it is tempting to think that anesthesiologists would not have made those mistakes, it is important to accept that every professional is vulnerable to human error. The doctor in the dental sedation disaster was an anesthesiologist.

In the Netherlands there have been three severe accidents in the last decade (2 with a fatal outcome and 1 with permanent neurological damage) in hospitalized children during sedation for MRI scanning. In all cases, sedation was provided by nonanesthesiologists, using combinations of long-acting sedatives. Health Inspectorate's investigation clearly showed that existing safety guidelines were not implemented in these cases. The question rose whether these

were isolated incidents. Subsequently, adherence to safety guidelines on pediatric procedural sedation in all hospitals in the Netherlands was investigated; adherence was not high and was unsatisfactory [23]. A nationwide survey of pediatricians queried their adherence to Pediatric Sedation (PS) safety guidelines. These guidelines were divided into presedation assessment, monitoring during PS, recovery and facilities, and competencies for emergencies and rescue. Pediatricians from 88 of the 97 Dutch hospitals responded. Less than 25% of respondents adhered fully to safety guidelines [24].

In a pilot survey among European pediatric anesthesiologists, we have found that similar accidents have happened elsewhere although none have been published. The exact characteristics of sedation practices by nonanesthesiologists have not been studied systematically but we believe that unsafe practice is still widespread [25].

Monitoring

Capnography and level of consciousness monitoring are probably less frequently used in Europe as compared to the United States. Capnography is useful, that cannot be denied, but probably its general use in sedated patients may not be widespread. A study from Turkey promotes its value in maintaining safety [26]. Limitations to its adoption have included limited financial resources. BIS and other monitors are scarcely used in the operating rooms for children; yet, they do have a place in the management of children who cannot tolerate standard anesthesia [27].

Recommendations

Anesthesiologists throughout the world have been quick to state the problems of sedation by the *untrained* and have published guidelines to prevent disasters. Excluding dentistry, the UK guidelines focused first on the Radiology setting [28] and then in 2001 the Academy of Medical Colleges responded to reports of unacceptable mortality in adult patients having esophago-gastroscopy [29]. They stated clearly, that "organizations should ensure that staff receive sedation training." The Scottish Intercollegiate Guidelines Network [30] gathered a body of opinion from across many specialties and developed a clinical guideline that has been quoted and used widely. In Italy, a fine review and guideline was produced for pediatric neuroradiology [31]. A guideline for nonanesthesiologists has been published for application throughout Europe [32]. However, in our own survey most respondents were not aware of any national or European guideline. National guidelines are available in the UK, Netherlands, and France.

Had any of these guidelines been applied, the aforementioned disasters would not have happened. Although these guidelines may have already, prevented many catastrophes, in the authors' opinion they would benefit from endorsement and dissemination by the specialty organizations. The dentists have progressed the most in sedation management and their efforts are discussed later. Capnography, properly applied, would have warned of a respiratory problem and may have avoided fatal outcomes.

Definitions

Initially, *conscious sedation* was an accepted endpoint or landmark in the continuum of conscious level. *Conscious*, meaning able to respond to the spoken word, has been replaced by the term *moderate sedation* in the current literature because it does not assume consciousness but rather that the patient is easily roused – usually by communication but also by other similar appropriate light stimulus [33]. Nevertheless, conscious sedation remains a common term [28, 34]. In the UK, dentists prefer the term conscious sedation because they define this as a level of sedation at which the patient responds easily to commands rather than any other stimulus.

The term *deep sedation* was not approved [28] and still is not in some professional groups, because it was indistinguishable from anesthesia. While this point may be overstated, it has led to the recommendation that both deep sedation and anesthesia must be managed by the same personnel,

equipment, and facilities. The definition therefore becomes more useful as a description of the intended conscious level rather than as a division on the basis of resources or risk. In a similar desire, two other descriptions of deep sedation/anesthesia have been used. Light anesthesia [35] or minimal anesthesia [36] are terms that could be used to describe a technique in which the patient seems unconscious although any appreciable stimulation is likely to rouse them. Propofol or sevoflurane [37] have been used to provide conditions with sufficient immobility for painless imaging.

Dissociative sedation is not a term in common use, but it is understood. Ketamine sedation or anesthesia is preferred generally.

Relative analgesia (RA) is a term intended to describe the analgesia and mild euphoria and calming properties of 30% nitrous oxide. Dentists have become expert in its use [38].

The question remains how well these definitions reflect reality and to what extent the outcome level can be predicted, especially when non-titratable drugs are used. These questions are relevant since procedural sedation by nonanesthesiologists is often performed using long-acting, nonintravenously administered medications. Motas showed that common drugs (e.g., chloral hydrate, midazolam, pentobarbital) in average doses cause wide variations in depth of sedation [39]. The goal of either conscious or deep sedation was not achieved in a significant number of children. Considering sedation levels as a sliding scale, rather than a step-by-step decline of consciousness, the Dutch working group on Procedural sedation decided to define in their new evidence-based guideline the same safety precautions for all levels beyond anxiolysis/mild sedation (www.cbo.nl).

Training and Credentialing

With the exception of dental sedation, there are no national training programs or qualifications for sedation. It is difficult to design a universal training schedule for the many different types of sedation, some of which will not be relevant for specialists. Four strategies that could move us towards credentialing have been clearly identified by Krauss and Green. [40] We favor the option of creating a safe and effective service controlled by the institution who takes their direction from national and professional guidelines. Such a system should bring development of efficient training that may evolve into national training schedules.

A seemingly straightforward skill that all sedationists should have is airway management and resuscitation. Access to live patients is a limiting factor and the development of life-like manikins is a potential solution. European resuscitation courses are widespread but do not aim to teach the monitoring and proactive airway skills that sedationists need. This should be a common component of specialty-specific sedation training courses.

Implementation

Several implementation factors separate Europe from the US. European standards of practice are mainly enforced by professionals themselves, whereas in the US the aspirations of professionals are enforced by financial penalty by insurance companies who demand that standards are maintained. In the UK, the National Institute of Clinical Excellence and Healthcare are producing guidelines for specific clinical problems and these will be enforced by government directive as well as by financial penalty to Hospitals. Clinical Governance is a term applied in the UK NHS to force individuals to bear responsibility for their actions and make sure that someone is accountable for failings in the service; it has helped improve quality and safety.

The number of malpractice actions is reputed to be highest in the US and the threat of financial loss and public distrust has been a driver for change. The publication of the US closed claims analyses has been very helpful and although defense organizations publish case studies and recommendations, there is nothing in that scale available in Europe.

In the Netherlands, and elsewhere, the implementation of guidelines on Procedural Sedation

and Analgesia (PSA) has been encouraged by raising public awareness through media and charities.

Common European Sedation Practice for Selected Procedures

Radiology

Painless Imaging

Both continents have tried to maximize the use of sedation for painless imaging. Nurse-led services for example were promoted as a practical alternative to anesthesia [41, 42]. Chloral hydrate [43] or Triclofos [44] have been the mainstay for children under 15 kg and have very good safety and success records; safety depends upon the user more than the drug; 95% of children fall asleep within one hour and remain asleep for approximately 45 min. In older children, few drugs are as effective, leading most hospitals to abandon sedation in this group [45]. Pentobarbital was withdrawn in the UK in the 1960s due to its potential for abuse. Secobarbital has been used but causes paradoxical reactions (as in pentobarbital). Dexmedetomidine, although not widely available in Europe was trialed in Turkey [46, 47]. So-called lytic cocktails are still commonly in use in the Netherlands.

The unreliable nature of sedation has caused many, if not most, hospitals to develop anesthesia led services [48] because there is a general acceptance that anesthesia is more efficient and maybe safer [49]. Certainly propofol [50] and sevoflurane [37] are standard techniques that are compatible with rapid recovery to street-fitness. Propofol may need to be combined with other drugs to maintain immobility and recently a combination of midazolam, nalbuphine and low dose propofol has been found to be reliable [51].

Interventional Radiology and Cardiology

Many intravenous lines can be inserted with a combination of moderate sedation and behavioral techniques; however, this requires appreciable effort to select children who can tolerate this course. Ketamine may be an alternative technique but we believe that interventional radiology is more readily managed by an anesthesia service because of its flexibility and the ability to overcome almost any problem. For cardiology some countries have managed to maintain an effective sedation service using a range of techniques involving combinations of propofol [52], ketamine [53], and remifentanil [54], but our view is that the practice of controlled ventilation using tracheal intubation and standard anesthesia techniques is more reliable and creates optimal conditions for imaging and measurements [27, 55].

Gastroenterology

We believe that many hospitals in Europe use sedation for endoscopy with a combination of benzodiazepines and opioids [56]. Surveys in both the Netherlands and the UK showed that 50% of endoscopies in nonuniversity hospitals are performed under this regimen. If there have been few problems, this is a credit to the judgment of gastroenterologists because the literature suggests that sedation is difficult especially for esophagoscopy [57]. It is likely that most practitioners prefer anesthesia [58]. An exciting development for gastroenterologists is the use of propofol without tracheal intubation for upper and lower endoscopies [45]. Some anesthesiologists are confident that this is a safe approach [19, 45, 59, 60] provided the gag reflex is not completely suppressed during upper endoscopy; lower endoscopy needs much less propofol except when the ascending colon, the cecum, and the terminal ileum are entered (a small dose of opioid may be useful at these times). Not only is this technique a reliable and safe alternative to benzodiazepine-based sedation, but it radically increases the patient throughput. In financial terms, this technique seems unbeatable. However, there may be many circumstances when it is not appropriate and many anesthesiologists believe that a technique involving tracheal intubation remains the safest of all.

Propofol, remifentanil, and desflurane could be used in a technique that is equally rapid (especially for colonoscopies).

Oncology

Many techniques are possible for children who need repeated painful oncology procedures. With practice, nitrous oxide alone is potentially useful. In most countries we believe that intravenous anesthesia is preferred [61]. Without anesthesia services, ketamine is a reliable technique. The addition of a short acting opioid to propofol is probably a common technique because it reduces the dose of propofol. Propofol with remifentanil has the potential to provide the most rapid technique. The apnea that it can cause indicates that the child will remain immobile during the procedure, albeit with assisted ventilation [62].

Emergency Medical Care

Procedural sedation and analgesia is being developed and applied on both sides of the Atlantic. There seems to be a gradual but steady progression by Emergency Physicians to develop their own standards and protocols such that in Europe and in the US, hospitals support the use of ketamine [63], opioids, and propofol to manage children for minor procedures. There may be a trend for emergency departments becoming focused on quality and safety. However, PSA is currently not incorporated in European training programs. A recent European study showed that in most Pediatric Emergency Departments (PED), PSA is practiced to the level of mild to moderate sedation. In about 20% of the PEDs deep sedation is not provided by the staff, while 7.5% of departments had no PSA available for their patients [64].

Alternatively, some hospitals have made extra efforts to provide anesthesia services, usually at fixed times of the day, to meet maximum demand [65]. In the UK, a ketamine protocol has been produce by the College of Emergency Physicians (http://www.collemergencymed.ac.uk/CEC/cec_ketamine.pdf); it is clear and explicit.

Dentistry

Dentists were pioneers of sedation and many are expert in their practice. They know that during conscious (moderate) sedation the patient should be rousable by verbal command but in addition they have observed that the mouth closes during deeper sedation. To keep the mouth open is a voluntary action and therefore mouth closure warns the dentist of a potential problem with the airway. It is important therefore to not use a mouth prop to keep the mouth open during sedation. Effective local anesthesia should make sedation much easier [66] yet many patients are fearful of the pain of needles in the mouth. For patients who will not, despite all behavioral techniques, accept the insertion of local anesthesia, sedation deeper than mild sedation is probably necessary. Mild sedation rarely, if ever, changes a *yes* to a *no*.

Nitrous oxide relative analgesia (RA) has been popular because it is remarkably safe and surprisingly well tolerated by children [67]. Dental "gas" machines are designed with devices to protect the patient against hypoxic gas mixtures and the breathing system connects to a nasal mask from which scavenging is possible. In children who tolerate nitrous oxide, gas mixtures with less than 30% nitrous oxide are almost always effective. More than this causes dysphoria, dizziness, and nausea [38]. Recommendations accept that hypoxia is so unlikely that pulse oximetry and fasting are unnecessary (large meals beforehand are discouraged however) [68]. Nitrous oxide given in a 1:1 mix with oxygen has been used in many children for a variety of procedures [6]. Hypoxia was rare, as was any airway obstruction and these problems only occurred when the patient had a cerebral disorder or was having another sedative drug [7]. Furthermore, in obstetric practice, fasting and pulse oximetry are not required during nitrous oxide analgesia (although nitrous oxide is self administered via a demand valve in contrast to the free flow apparatus used in Belgium and France).

Standard sedation for children is limited to RA in most parts of Europe [69]. When nitrous oxide is insufficient to calm a patient, other drugs have been added. These may *tip* the patient into deep sedation, which is an obvious hazard, even though the risk may be small. In a study comparing RA with a combination of RA and 0.1–0.3% sevoflurane, the dental treatment was completed in 52% and 89%, respectively. The same team, in another study, found that sevoflurane (0.3%) added to nitrous oxide (40%) and intravenous midazolam was effective in 93% (249/267) of anxious children who would have been given general anesthesia otherwise [70]. All children remained rousable and none required airway management or oxygen – nevertheless, all children were fasted and monitored and these techniques were delivered by trained anesthesia personnel in a specialist dental clinic.

Other dentists have tried oral drugs. Oral and rectal benzodiazepines are commonplace in Sweden [71]. Midazolam is often useful to calm children [72] but treatment may have to be limited to minor restorations only [73]. In uncooperative toddlers (2–4-year old) a cocktail of chloral hydrate, meperidine, and hydroxyzine was effective in only 72% and adverse conditions including vomiting, desaturation, prolonged sedation, and an apneic event occurred in 3% of all sedations (but were reported as minor) [74].

Intravenous midazolam alone is recommended in the UK for anxiolysis in children over 16 [69] and may be appropriate and effective in younger adolescents [75]. Propofol has been used alone as a sedation technique but lacks the analgesic component to enable insertion of local anesthesia [76]. Consequently, intravenous cocktails containing midazolam, alfentanil, ketamine, and propofol are being explored [77, 78]. A recent review of experience in 1,000 cases shows that these drugs can be combined safely [79]; loss of verbal contact occurred in approximately 0.05% and nausea was a problem in 5%. Whether this "alternative" technique can be called sedation is debatable if it is unknown whether it will cause accidental anesthesia. Certainly, alfentanil can cause apnea when the pain of dental treatment has subsided [22].

Many of these specialist techniques may not be applicable outside specialist centers and there is some evidence to support the view that most dentists and anesthetists believe that uncooperative children should be managed with short acting anesthesia in a hospital setting [80, 81]. Recently, in the UK, a group of dentists have pressed for conscious sedation techniques to progress beyond the limits of RA (and benzodiazepines for adolescents). They now have recommendations to develop new sedation techniques using subanesthetic doses of potent anesthesia drugs. Time will show how safe these techniques are.

New and Future Developments

Training and accreditation are the most important objectives for sedationists around the world. Their skills need to be focused on the type of sedation that they need to administer and their protocols will need to restrict their practice to avoid unexpected problems. We believe that airway management and monitoring skills should be generic to any qualification.

A new guideline – **Sedation for diagnostic and therapeutic procedures in children and young people** – has been developed in the UK and published by NICE in December 2010 [82, 83]. NICE is the National Institute for Health and Clinical Excellence of the UK. These guidelines incorporated evidence of safety and efficacy of selected sedation drugs, consensus statements about patient management, and cost effectiveness considerations. Important deviations in these guidelines from those of the United States are the recognition of propofol and sevoflurane inhalation as agents appropriate for pediatric sedation [82] (Table 17.1). This NICE guideline is unique among other NICE guidelines because it specifies the principles of training needed to use effective sedation techniques safely. It states that healthcare professionals trained in the delivery of anesthesia may administer sevoflurane, propofol, or a combination of opioids with ketamine. A treatment pathway and sedation algorithm is detailed in Fig. 17.1 [82].

Table 17.1 Current licensing status for sedation drugs* (NICE Guidelines)

Drug	Indication	Licensed use (taken from the *British National Formulary for children (BNFc) 2010/11*[3])
Chloral hydrate	For mild to moderate sedation	Not licensed for sedation in painless procedures. For dosing (by mouth or by rectum) for painless procedures in children from neonates to 18 years, see the *BNFc*
Fentanyl	For analgesia and for improved anesthesia	Licensed for use in children older than 1 month with spontaneous respiration for analgesia, and during operations for improved anesthesia by intravenous injection over at least 30 seconds
	For moderate to deep sedation	If deep sedation is needed. a general anesthetic (e.g., propofol or ketamine) or a potent opioid (e.g., fentanyl) may be used; these should be used only under the supervision of a specialist experienced in the use of these drugs
Intranasal diamorphine	For mild to moderate sedation in managing acute pain and short painful procedures	Licensed for intranasal route but listed in the *BNFc* as follows: acute pain in an emergency setting or short painful procedures; intranasally in children heavier than 10 kg
Ketamine	Anesthesia	Licensed for use in anesthesia for all ages; intravenous and intramuscular
	Lower doses are used for moderate sedation	If deep sedation is needed, a general anesthetic (e.g., propofol or ketamine), or a potent opioid (e.g., fentanyl) may be used. However, they should be used only under the supervision of a specialist experienced in the use of these drugs
Midazolam	For mild to moderate (also referred to as conscious) sedation	Not licensed for use in children younger than 6 months for premedication and conscious sedation
		Not licensed for use by mouth or by buccal administration
		Intravenous midazolam is not licensed for use in children younger than 6 months for conscious sedation
		No UK marketing authorization for oral or intranasal midazolam for sedation. However, dosing for children from age 1 month is given in the *BNFc*
Morphine	Analgesia and for deep sedation	Licensed for analgesia in all ages; subcutaneous or intravenous. Other routes have restricted licensing; Oramorph solution (morphine) is not licensed for use in children younger than 1 year; Oramorph unit dose vials is not licensed for use in children younger than 6 years; Sevredol tablets (morphine) are not licensed for use in children younger than 3 year; MST continuous preparations (slow release morphine sulfate) are licensed to treat children with cancer pain (age range not specified by manufacture); MXL capsules (morphine) are not licensed for use in children younger than 1 year). If deep sedation is needed, a general anesthetic (e.g., propofol or ketamine) or a potent opioid (e.g., fentanyl) may be used; these should be used only under the supervision of a specialist experienced in the use of these drugs

(continued)

Table 17.1 (continued)

Drug	Indication	Licensed use (taken from the *British National Formulary for children (BNFc) 2010/11*[3])
Nitrous oxide	For minimal to moderate sedation during relatively short procedures	50% nitrous oxide licensed for use in sedation for all ages (inhalation); nitrous oxide in concentrations > 50% is not licensed for analgesia without loss of consciousness
Opioids	For moderate to deep sedation	If deep sedation is needed, a general anesthetic (e.g., propofol or ketamine) or a potent opioid (e.g., fentanyl) may be used; these should be used only under the supervision of a specialist experienced in the use of these drugs
Propofol	Anesthesia	Licensed for use in all children older than 1 month in intravenous doses of 0.5% or 1%
	For moderate to deep sedation	Licensed for use in people older than 17 years
		The Guideline Development Group decided to recommend off-label use of propofol for sedation in children of all ages. This was because propofol is widely used in the UK for sedation in children of all ages and the doses used for sedation are much lower than those used for anesthesia. If deep sedation is needed, a general anesthetic (e.g., propofol or ketamine) or a potent opioid (e.g., fentanyl) may be used; these should be used only under the supervision of a specialist experienced in the use of these drugs
Sevoflurane	Anesthesia	Licensed for use in anesthesia for all ages (inhalation)
	For moderate to deep sedation	Sedation is outside the licensed use

* These drugs have been recommended for pediatric sedation. Informed consent should be obtained and documented for the use of any drug outside the licensed indications
Source: Reproduced from Sury et al. [82], with permission from BJM Publishing Group Ltd

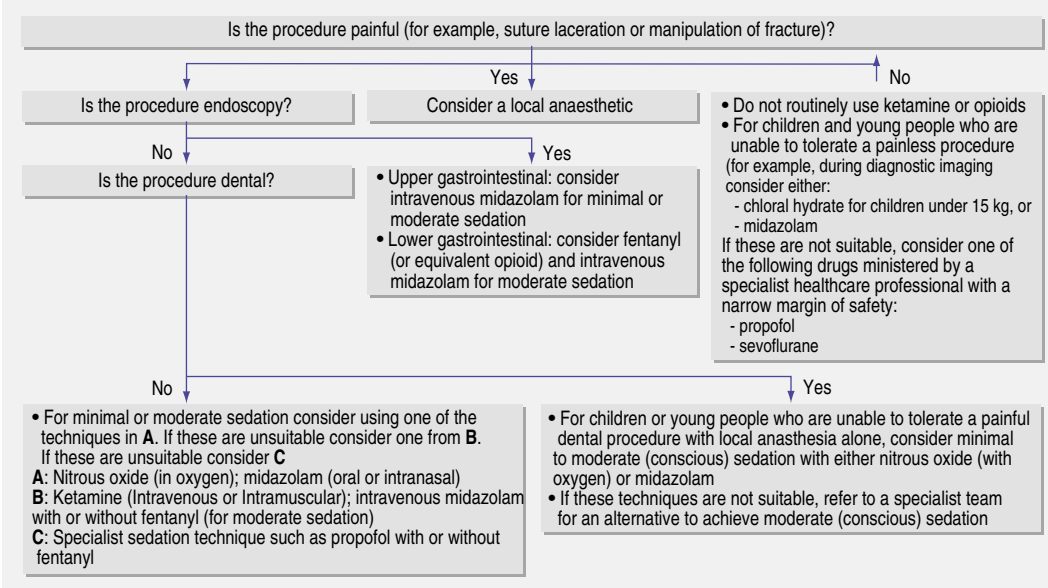

Fig. 17.1 Sedation algorithm and pathway (reproduced from Sury et al. [82], with permission from BJM Publishing Group Ltd)

In the Netherlands, the Dutch Institute for Healthcare Improvement (CBO) commissioned Pediatric Guidelines for Procedural Sedation and/or Analgesia (PSA) at Locations Outside the Operating Theatre from the Netherlands Society of Anesthesiologists and the Dutch Society of Pediatrics [84]. Recently published in 2011, the Guidelines were meant to represent six important cornerstones, notably including the optimal use of local or topical anesthesia, nonpharmacological techniques, and the prohibition of forced securing and restraint [84] (Table 17.2).

These Dutch guidelines were noteworthy because they distinguished deep sedation from dissociative sedation [84] (Table 17.3). Sedation of ASA III and IV patients by nonanesthesiologists

Table 17.2 Cornerstones of a comprehensive policy towards procedural comfort in Children, Dutch Institute for Healthcare Improvement

1. **Prevention** of procedural pain and stress
2. An active policy in relation to the **prevention of forced securing and restraint**
3. Optimal use of effective forms of **local or topical anesthesia**
4. The systematic application of effe**ctive non-pharmacological techniques** (preparation, distraction, hypnosis, etc.)
5. **The application o**f the **most adequate PSA technique**, individually titrated and carried out by a trained professional
6. A local policy towards the ready availability of the so-called "**rescue anesthesia"** if a PSA technique turns out to be inadequate or if it can be anticipated that the available PSA techniques may be insufficient or unsafe in an individual patient

Source: Reproduced with permission from [84]. Table 17.1. Note: The final version of the guidelines is pending approval by the Dutch Society of Pediatrics and the Dutch Society of Anesthesiology

Table 17.3 Definitions of different levels of sedation, Dutch Institute for Healthcare Improvement

1. *Light sedation/anxiolysis*: Two states that are difficult to tell apart, in which the anxiety and stress level of the patient have been lowered while the patient remains basically fully conscious. The patient responds adequately and consistently to verbal stimuli, and verbal communication therefore remains possible. This state is associated with few risks in patients without significant comorbidity. Although cognitive functions and coordination are reduced, ventilatory and cardiovascular functions remain unaffected. Light sedation/anxiolysis is typically a state of mind that occurs after 1 standard dose of midazolam (0.1 mg/kg intravenously *or* 0.2–0.5 mg/kg transmucosally) and with nitrous oxide sedation (inhalation concentration up to 50%). Higher doses, other medicines, and combinations with other analgesics will virtually always lead to a deeper sedation level
2. *Moderate sedation*: Pharmaceutically induced reduction in awareness, during which the patient still responds purposefully when spoken to, or to light tactile stimuli. In this stage, no interventions are needed to keep the airway open, airway reflexes are intact, and ventilation is adequate. If the response is not clearly adequate and purposeful but more of a withdrawal reflex, we speak of deep sedation
3. *Deep sedation*: This is a pharmaceutically induced decline in awareness, during which the patient does not respond to being spoken to, but reacts purposefully to repeated or painful stimuli. Airway reflexes and ventilation may be reduced and it may be necessary to keep the airway open. The concept of "deep sedation" is a contested term because the distinction with anesthesia becomes less clear. A typical example is the deep sedation caused by propofol, during which it is possible, with the necessary expertise, to keep spontaneous respiration going and the airway open. The risk of reduced breathing is more or less a linear function of the dose and depth of sedation
4. *Dissociative sedation*: Also called a trance-like cataleptic sedation, it is typically the result of sedation with ketamine. As far as the depth of sedation, analgesia, and response level is concerned, ketamine causes a state that primarily corresponds to anesthesia. However, contrary to anesthesia, the airway reflexes, respiration, and hemodynamics largely remain intact, even at comparatively high doses. It makes ketamine attractive for use in PSA, particularly for painful procedures
5. *General anesthesia*: A pharmaceutically induced state of unconsciousness, in which the patient is unresponsive, even to painful stimuli. The ability to keep the airway open will often be reduced or absent, and ventilation will frequently be depressed, consequently requiring support. Cardiovascular functions may also be impaired. Can only be applied under the personal supervision of an anesthesiologist

Source: Reproduced with permission from [84]. Table 17.2. Note: The final version of the guidelines is pending approval by the Dutch Society of Pediatrics and the Dutch Society of Anesthesiology

is discouraged and, if performed, should be done only after consultation with an anesthesiologist and by a specially trained and credentialed nonanesthesiologist. Fasting status (NPO) deviates from guidelines of other specialty societies in that light sedation does not need NPO status. An emergent, acute condition in a child who does not have an empty stomach is not an absolute contradiction for PSA [84] (Table 17.4).

Propofol, in the Dutch guidelines, although preferably administered by an anesthesiologist, may be delivered, by an experienced nonanesthesiologist for ASA I and ASA II patients. Patients of ASA III status and higher can only receive propofol from an anesthesiologist [84] (Table 17.5). These guidelines are unique in that they have specific recommendations which are procedure based: Gastrointestinal procedures in particular should favor propofol, if necessary in combination with midazolam or an opioid [84] (Table 17.6).

It is hoped both the NICE and Dutch initiatives will be a fresh attempt to consider the evidence about effective and safe sedation for children and that their output will further encourage an improvement in the services available to children in Europe and beyond.

Table 17.4 NPO fasting recommendations, Dutch institute for healthcare improvement

1. Fasting is not needed for children undergoing light sedation
2. A child must *preferably have an empty stomach* for any (elective) PSA with moderate or deep sedation, in accordance with the same guidelines that apply to interventions taking place under general anesthesia (two hours for clear liquids, four hours for breastfeeding, and six hours for other meals)
3. A child in an acute condition without an empty stomach is in itself *no absolute contra-indication* for PSA. This is important if postponing the procedure would pose health risks and/or discomfort. However, in that case the choking risks must always be carefully considered, taking into account the choice of sedative, the depth of sedation, and any protection of the airway. In practice, this amounts to the following recommendations
(a) With PSA in an acute situation (without an empty stomach), deep sedation must be avoided as much as possible, since the protective airway reflexes may be disturbed or there is a high risk of respiratory impairment (b) If a procedure requires a form of *deep* sedation, the patient must have an empty stomach (c) If a procedure requiring a form of deep sedation is urgently needed and an empty stomach can therefore not be guaranteed, deep sedation must performed under the supervision of an anesthesiologist in order to ensure optimal protection of the airway
4. Not having an empty stomach must be no reason or excuse for performing a procedure with an ineffective form of light or moderate sedation

Source: Reproduced with permission from [84]. Recommendation 10. Note: The final version of the guidelines is pending approval by the Dutch Society of Pediatrics and the Dutch Society of Anesthesiology

Table 17.5 Propofol recommendations, Dutch institute for healthcare improvement

Propofol is suitable for application in (urgent) painful procedures in children. Propofol causes deep sedation to anesthesia. The preconditions on patient selection, skills, competencies, monitoring, and the other preconditions set out in part I of this guideline must therefore be complied with. Since propofol is a fast-acting, very potent medicine that can quickly lead to oversedation and respiratory depression in untrained hands, the working group also has the following recommendations:
1. The person who performs the PSA must never be the same person as the one carrying out the procedure or intervention
2. The PSA is preferably carried out by an anesthesiologist
3. If the PSA with propofol is carried out by a nonanesthesiologist, it must be performed by a physician who has already been working with the medicine for a longer period of time and who is able to assess and deal with any respiratory complications
4. PSA with propofol in patients of ASA class III or higher must be performed by an anesthesiologist
5. Preoxygenation and monitoring through capnography with PSA using propofol is strongly encouraged in order to restrict the comparatively high risk of respiratory complications

Source: Reproduced with permission from [84]. Note: The final version of the guidelines is pending approval by the Dutch Society of Pediatrics and the Dutch Society of Anesthesiology

Table 17.6 Sedation recommendations for GI procedures, Dutch institute for healthcare improvement

1. A gastrointestinal (GI) endoscopic examination in a child must be carried out in principle under general anesthesia or deep sedation. If it is decided to opt for deep sedation, then titratable medicines must be used that are certain to lead to an effective level of deep sedation. Of all the medicines studied, propofol is the most effective, if necessary in combination with midazolam or an opiate
2. The working group advises against the following forms of PSA for GI endoscopic examinations:
Using ketamine for endoscopic examinations of the esophagus, stomach, and duodenum, since there is an increased risk of laryngospasm Using a benzodiazepine on its own or the combination of benzodiazepine with an opiate. Both forms of PSA are substantially less effective than anesthesia or deep sedation with propofol Benzodiazepines must not be considered as suitable medicines to generate a reliable level of amnesia for endoscopic procedures
3. As far as rectoscopies are concerned, it is worth contemplating whether the investigation could be carried out without PSA insofar as informed consent has been obtained and provided the child is not scared or opposed to the examination
4. If general anesthesia or the support of an anesthesiologist are not feasible, an endoscopic department must have access to the logistic possibilities as well as trained professionals in order to provide safe and effective deep sedation that fulfills the preconditions of these guidelines
5. Premedication with midazolam taken orally can be considered prior to deep sedation. It reduces stress levels for inserting the drip at the start of the procedure and may therefore result in a smaller dose of propofol being required

Source: Reproduced with permission from [84]. Note: The final version of the guidelines is pending approval by the Dutch Society of Pediatrics and the Dutch Society of Anesthesiology

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18 Pediatric Sedation in the Underdeveloped Third World: An African Perspective: Models, Protocols, and Challenges

James A. Roelofse

Introduction

Pediatric sedation for diagnostic and surgical procedures outside the operating room remains a controversial issue worldwide. Healthcare centers are, however, experiencing an increasing demand in this regard. The stage may even have been reached where the number of children requiring sedation outside the operating room may be approaching the number of children requiring general anesthesia. Pediatric sedation is probably one of the fastest growing areas in patient care as it can in appropriate situations offer a safe alternative to anesthesia in operating rooms of limited capacity. One of the challenges is that children probably represent a population with the highest risk/lowest error tolerance.

Pediatric sedation services can be defined as the formal allocation of identifiable resources and providers in order to provide scheduled sedation for children at various locations outside the operating room [1]. A wide variety of specialties and subspecialties, anesthesiologists as well as nonanesthesiologists, are involved in pediatric sedation, utilizing different drugs and administered by different routes. There is probably little agreement as to who should be the sedation provider or on the drugs to be administered, the techniques employed, the practice settings, and what support staff should be involved in pediatric sedation outside the operating room. Unfortunately, few institutions have dedicated and structured pediatric sedation services in spite of the recommendations from various organizations in this regard [2].

Sub-Saharan Africa is a densely populated and resource-poor subcontinent and has unique challenges in patient care, including a lack of sufficient facilities and staff for performing operations in the traditional operating room. Therefore, a growing demand for sedation services for procedures outside the operating room exists and it will most probably continue to increase, especially in the rural areas of Africa. Pediatric sedation will thus be a big plus factor in providing affordable health care for certain procedures in such settings. Training in pediatric sedation services remains a major obstacle and very few centres in Africa provide structured pediatric sedation training, let alone structures for the maintenance of competencies at all levels. A system is needed that can accredit individual sedation practitioners and training must be expanded to include other healthcare professionals in order to meet this growing demand for sedation services. This is not a simple process because of the shortage of resources and the vast distances people have to travel in order to receive training and to maintain their clinical competence.

The shortage of healthcare professionals to provide sedation services outside the operating room needs to be addressed. There are simply not

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enough trained healthcare professionals available to meet these demands and, with an ever-growing population and the attending economic realities, this is not about to change. A lack of knowledge on sedation and a lack of understanding that pediatric sedation can be a safe alternative to general anesthesia for certain procedures outside the operating room, hampers the development of structured sedation services in most countries around the world. Information on the value of sedation should be made available in order to help inform healthcare personnel on sedation as a safe alternative to general anesthesia. In addition, more training opportunities for sedation practitioners should be created. This is only possible by the enthusiastic collaboration between the discipline of anesthesiology and other relevant healthcare disciplines/subdisciplines, especially in far-flung areas such as rural Africa with its unique problems. More research is necessary at university level, with international collaboration, to assess the use of drugs and drug combinations that can be used for safe pediatric sedation outside the operating room in such circumstances.

The demand for sedation for procedures on children outside the operating room already seems to exceed the capacity for offering anesthetic services in the operating room. This is a serious problem that will have to be addressed to ensure that sufficient sedation providers are available to provide sedation services, and sufficient anesthesiologists to provide anesthetic services, especially in resource-poor settings. The shortage of providers and lack of training is probably the most common barrier to the development of universal pediatric sedation services. In an effort to address the problem, this author has spent the last decade and more in developing training programs for sedation practitioners and in developing protocols for safe sedation services. The results of these endeavors are outlined below.

Sedation Training

Sedation training in Africa, on an organized and structured basis, was nonexistent before the year 2000. Since then a Postgraduate Diploma in Sedation and Pain Control has been offered in South Africa to anesthesiologists and nonanesthesiologists in the principles and techniques of both pediatric and adult sedation, first at Stellenbosch University and later the University of the Western Cape. Anesthesiologists and dentists are trainers for this part-time modular program, which is presented over 2 years. During the first year of training, three contact sessions lasting 3 full days each are held – this period is spent on both theoretical and practical training, and involves both medical and dental cases for sedation. All students must have an Advanced Adult Life Support and Advanced Pediatric Life Support certification before they can proceed to the second year of training. Certification must be updated regularly.

The second year of training involves again theoretical and practical training. Students must then also write a 5,000 word referenced dissertation on a topic related to sedation and pain control. Students are encouraged to visit the University of the Western Cape at regular intervals during the 2 years of study in order to acquire more practical training in other related areas of sedation and pain control. Students in possession of the diploma in sedation and pain control can then proceed to do a research Masters degree. The diploma and Masters programs attract students from all corners of Africa, and even from other countries outside Africa, as few structured sedation training programs are available elsewhere. The majority of our students are nonanesthesiologists, usually medical practitioners with a special interest in sedation practice – the self-proclaimed "professional sedation practitioners." This is a career pathway for them. Subsequently, other areas of Africa have requested development of similar sedation programs. The author has since initiated sedation training at universities in Nairobi, Kenya, and at institutions in other African states. Healthcare providers across Africa now recognize that sedation offers an acceptable alternative to general anesthesia for some various and diverse procedures.

As interest in creating formal sedation training programs grows, centers in developed countries are initiating sedation training programs. A collaboration with University College London in the United Kingdom has been established,

directed and taught by Dr. James Roelofse, the founder of the South African Postgraduate Diplomas in Sedation. A Postgraduate Certificate in Sedation and pain Control is now offered in London.

A review of world-wide opinions and guidelines begs an important question. Who qualifies for sedation training, i.e., are nonanesthesiologists in the developing nations with limited resources capable of providing safe sedation to children? [3] Particularly, in underdeveloped countries, anesthesiologists are limited. Healthcare practitioners would need to be trained as pediatric sedation providers to meet the growing need [2]. Therefore, nonanesthesiologists are accepted into the abovementioned training programs, as they can play a vital role in providing sedation services, particularly in rural areas. Almost all the nonanesthesiologists on our course, apart from dentists, have a diploma in anesthesia from the College of Medicine of South Africa. Everyone is required to have training in anesthesia. Nonanesthesiologists and anesthesiologists receive the same training for the diploma program. The diploma program provides didactics on all matters related to safe sedation practice and emphasizes that only ASA I and II patients qualify for their care. The collaboration of anesthesiologists to train and educate nonanesthesia caregivers to safely sedate a clearly identified pediatric population (ASA I and II) is an important first step in Africa. By being involved in the training of nonanesthesiologists, the specialty of anesthesia will retain its influence on the quality and direction of patient care and sedation practice.

Complicated multidrug sedation techniques are not always necessary for children. All healthcare professionals involved in pediatric sedation must be trained in specific sedation techniques and must follow the accepted guidelines and protocols. Even anesthesiologists should be trained in specific sedation techniques i.e., in dentistry. This view was endorsed in 2007 by the Royal College of Anesthetists and the Faculty of Dental Surgery of the Royal College of Surgeons of England: The Standing Dental Committee in the United Kingdom published their guidelines on the "Standards for Conscious Sedation in Dentistry: Alternative Techniques" [4]. The guidelines state that it is essential that there is "evidence of training (even for anesthesiologists) in specific alternative sedation techniques, in an appropriate environment." Children under 12 years of age are specifically mentioned as a group for whom sedation providers must receive formal training. The American Society of Anesthesiologists (ASA) has published guidelines for sedation services provided by nonanesthesiologists [5], and the guidelines have been endorsed by the American Academy of Pediatrics (AAP), and the Joint Commission [6–8].

Sedation Models

To find an acceptable pediatric sedation model that suits every case is difficult. Children undergoing diagnostic or therapeutic procedures are usually frightened and uncooperative. Anxiety and fear may be exacerbated by many different stressors especially previous unpleasant experiences. The need to provide analgesia together with sedation for painful procedures has resulted in the proliferation of many pharmacological agents used in combination. Polypharmacy, with its possible adverse events/complications for the untrained, has become commonplace especially for painful procedures. Sedation provider services outside the operating room are in demand inside the hospital environment, in the office/surgery, or in other facilities that meet all the requirements for safe sedation practice [2].

The various pediatric sedation models that have been established throughout Africa will be reviewed below.

The Sedation Unit Model Within the Hospital

This model allocates a designated area of the hospital as a sedation room and a recovery area, which together represent an area for sedation, the procedure, and recovery. Training in a designated sedation unit makes students appreciative of this ideal environment for safe sedation practice.

This designated area most commonly provides dental sedation and is adjacent to the operating room should a failed sedation case need to progress to general anesthesia. Children receive oral or transmucosal sedation in the recovery area and are then transported to the sedation room, and back to the recovery area after the procedure. The area also has a nitrous oxide/oxygen unit, including a separate portable nitrous oxide/oxygen unit with a sevoflurane vaporizer. Low concentrations of sevoflurane (0.3%) can be added for very anxious children, delivered by trained nonanesthesiologists. Parents/escorts are allowed to accompany the child into the sedation room until the child is comfortable, but must leave once the procedure is commenced.

We have primarily embraced the pediatric dental model for training purposes – this is a unique model as the airway is shared by both the sedation practitioner and the surgeon. This is an ideal situation for training safe sedation techniques. In our sedation unit, we provide intravenous sedation for over 800 cases a year. Only ASA I and II patients are done outside the operating room in our unit.

Pediatric dental care is still a problem in developing countries as in Africa. Many of the pediatric cases we do under intravenous sedation need extensive dental surgery. Longer periods of intravenous sedation using a variety of agents are often necessary to complete the work. It is sometimes impossible to do dental fillings because of extensive damage to teeth – multiple extractions are often necessary. Our sedation unit is a day-care facility. The sedation unit is staffed by both anesthesiologists and nonanesthesiologists who work in the unit on a part-time basis. Funding for the actual sedation service is provided by the government and the university.

The Mobile Sedation Model Within the Hospital

This model requires that sedation providers, i.e., both anesthesiologists and nonanesthesiologists, render a sedation service at a distant site within the hospital. This site is usually proximal to the inpatient hospital wards. For this, they use portable sedation equipment and the appropriate drugs for sedating children in multiple locations in the hospital, e.g., for bone marrow biopsies [9]. Children are sedated, receive the procedure, and recover at the site of the procedure by the sedation provider and support staff. This approach avoids the need for the transport of the sedated child between the ward and procedure area.

A Combined Sedation Model Within the Hospital

A combination of the above-mentioned two models allows that some children are sedated in the unit and transported to fixed facilities, e.g., MRI imaging. The sedation unit is reserved for those procedures that may be performed on-site.

The Mobile Sedationist Model Outside the Hospital

A model that is growing, albeit controversial, is administration of sedation in the office or ambulatory center by a "mobile sedationist." Mobile sedationists are especially popular for pediatric dental procedures and provide the dental practitioner with the opportunity to do procedures in a familiar environment equipped with his own specialized equipment. This is a cost-effective approach as it avoids the add-on costs generated when such procedures are performed in hospital operating rooms. This approach could potentially have substantial economic benefits for patients and their health insurance companies. As hospital-associated costs escalate, the demand for mobile sedationists by different specialists, such as dermatologists and plastic surgeons, is increasing. This development in pediatric sedation services makes structured training in specific pediatric sedation techniques even more crucial. One concern is at what age can one safely sedate a child in a remote setting? In South Africa, the mobile sedationist model is reserved only for ASA I and II children and delivered by healthcare professionals appropriately trained in all areas of safe pediatric sedation practice.

The Operator-Sedationist Model

This model does not conform to guidelines and policies of some specialty societies outside of Africa. However, it tends to be used for simple procedures. In this model, the sedation provider also performs the procedure. This model is practiced by dentists and other healthcare professionals, usually administering nitrous oxide/oxygen inhalation sedation for dental procedures, the suturing of lacerations, application of burn dressings, cannulation of veins, etc. In the author's view, the activities of operator-sedationists should be confined to the use of single drugs, reserving combination drug therapy to the dedicated sedation provider model such as that presented in the mobile sedationist model previously. The usual techniques for pediatric sedation by operator-sedationists include standard sedation techniques with nitrous oxide/oxygen or oral/transmucosal benzodiazepines [4]. Intravenous routes of sedation delivery are not generally used by operator-sedationists. This model clearly has its restrictions and tends to offer sedation for a small group of children undergoing a limited type of procedure.

The Dedicated Sedationist Model

More advanced alternative techniques of sedation delivery, which include continuous infusion of drugs, target-controlled infusions, and multi-drug therapy, are only used by dedicated sedationists in Africa. Members of a pediatric sedation team using such alternative techniques must include at least two suitably qualified and experienced people. The techniques are especially valuable for painful and more complicated procedures, as there is no single agent that meets all the requirements of an ideal agent.

African Guidelines for Safe Pediatric Sedation

Safe pediatric sedation requires that established guidelines be rigorously followed. Sedation practitioners doing sedation outside the operating room are advised to follow the guidelines of the American Academy of Pediatrics (AAP), the American Society of Anesthesiologists (ASA), and the Joint Commission [5–7, 10, 11]. The pediatric sedation guidelines from the South African Society of Anaesthesiologists have recently been published [12]. These guidelines recognize deep sedation as part of the spectrum of general anesthesia, only to be administered by trained anesthetists. Sedation of children <3 years of age is recommended only to be performed by practitioners with extensive experience. Pre-sedation evaluation is emphasized and the airway evaluation (physical and clinical history) will direct the triage decision. Those with specific airway factors should be restricted to sedation in hospital only (Table 18.1). Only ASA I and ASA II patients may be sedated outside the operating room. Fasting guidelines follow 2 h for clear fluids, 4 h for breast milk, and 6 h for formula and solid food. Nitrous oxide (50%) does not require fasting of any limit. Propofol is identified as a sedative hypnotic and may be administered by an "experienced sedationist skilled in airway management," with capnography highly recommended.

Table 18.1 Specific airway factors that exclude sedation outside the in-hospital setting

Children with obstructive sleep apnoea (OSA)
Children with known large tonsils approaching the midline or associated with loud snoring
Children who cannot lie flat because of airway obstruction
Children with stridor
Retropharyngeal masses
Neck masses
Tracheal deviation
Mallampati >2
Neck mobility – decreased range of movement including a hydrocephalus with a large head
Syndromic features (Pierre-Robin, Treacher-Collins)
Enlarged tongue
Micrognathia
Abnormal ears
Beware of the child with malignancy – multiple level airway obstruction possible
Haemangiomas

Source: From Reed et al. [12]. Reprinted with permission

Table 18.2 Dosing schedule for "Ketofol"

Route	Dose	Onset	Duration of action	Repeat dose	Titration interval
IV	0.05 ml/kg[a]	30–90 s	5–10 min	0.05 ml/kg	1–5 min

Ketofol: 5 mg/ml Ketamine, 9 mg/ml Propofol
[a]0.25 mg/kg ketamine and 0.045 mg/kg propofol
Source: From Reed et al. [12]. Reprinted with permission

Ketofol is identified as a combination of ketamine and propofol that work synergistically and may be administered as Boluses (Table 18.2); 50 mg ketamine with 90 mg propofol diluted to 10 ml is the recommended preparation for a 5-mg/ml ketamine and 9 mg/ml propofol concentration. These guidelines do not approve of remifentanil sedation for children but do sanction fentanyl and alfentanil in combination with other sedatives.

The qualifications of sedation providers are recommended to include core training in sedation technique in addition to knowledge of anatomy, monitoring, airway examinations, and ability to rescue.

The safe practice of pediatric sedation has three very important components:

- *Pre-sedation assessment*, which is a critical component to exclude patient states that may affect the risk of sedation or may be a contraindication to sedation outside the operating room.
- *Sedation for the planned procedure*, attention should be focused on safe premises; the equipment; the actual sedation process with its various aspects including monitoring, selection and administration of drugs; and documentation.
- *Recovery and discharge criteria*, which may be the weakest link in pediatric sedation practice.
- Hoffman et al. [13] structured a system for pediatric procedural sedation by nonanesthesiologists using a model based on ASA and AAP guidelines. This system includes a sedation plan and a method for the identification of risk factors for sedation – colloquially referred to as "red flags" – that must be taken into consideration before starting the sedation process. This is a very useful system to follow. A training program for pediatric sedation techniques, outside the operating room, emphasizes the need to have such a protocol in place and to rigidly adhere thereto.

In all cases, special attention must be paid to the following [4]:

- *Documentation and protocols* must comply with contemporary guidance [4, 6, 11]. This includes documentation before, during, and after sedation. Particular attention must be paid to pre-sedation assessment and the identification of risk factors for sedation. Written informed consent must be obtained and verbal and written instructions for, before and after the sedation procedure must be conveyed to a responsible person. No child should be sedated without an escort being available to accompany the child home. All the parameters that are monitored during sedation must be fully documented and any adverse events must be entered on the sedation chart.
- *Facilities* must comply with the standards required for safe pediatric sedation outside the operating room. Attention should be focused on the procedure room where the appropriate staff and equipment must be available to monitor and rescue a child. Recovery facilities must meet all the requirements for safe recovery of the child after sedation. A protocol for back-up emergency services must be available for all cases done outside the operating room and ready access to ambulance services is advised whenever pediatric sedation is done.
- *Equipment* for pediatric sedation should be appropriate for the intended procedure as well as the targeted depth of sedation. Monitoring equipment for all but the simple single agent (oral or inhalation) technique should include ECG, blood pressure, and pulse oximetry. If available, an end-tidal carbon dioxide monitor

should be used. Precordial stethoscope remains an inexpensive and practical monitor, especially in rural settings, which lacks resources. It is advisable to have a defibrillator on hand whenever pediatric sedation is done outside the operating room, especially when combined drug techniques are employed.

- The *team concept* is an important aspect of pediatric sedation. The team must include either the operator-sedationist (for standard sedation techniques) or a dedicated sedationist, and support staff. Support staff is required to assist with monitoring of the patient and must be able to render active support if the need for rescue should arise.

The question remains, however, what guidance is available to equip the mobile pediatric sedationist who travels to a distant facility/office in order to provide a safe pediatric sedation service. The protocol for safe practice requires that the mobile sedationist must understand that he/she is responsible to ensure that the premises meet all the requirements for safe sedation practice, and also for pre-sedation assessment, intra-operative care, and postoperative discharge of the child. The sedation practitioner must be assisted by suitably qualified healthcare professionals who can assist with monitoring and rescue, if necessary.

A novel approach to sedation preparation adopts the terminology "hardware" and "software." It is essential that the mobile sedation practitioner has both the necessary "software" and "hardware" available to provide a safe pediatric sedation service. The "software" includes training, skills, and experience that are crucial to safe practice. A mobile sedationist must also have access to the appropriate office infrastructure. This includes secretarial services to take care of appointments, the preparation of all the paperwork that should be sent to the parents ahead of time in respect of pre- and postoperative instructions, and to gather information regarding the health status of the child. A patient follow-up system should be in place to allow the parent/guardian to give postoperative feedback. The questionnaire allows for feedback on patient satisfaction and possible side-effects, inclusive of postoperative nausea and vomiting, pain during the procedure, double vision, and emotional disturbances. The form also invites comment as to whether the parent/child would prefer sedation again, or rather opt for general anesthesia. This assists the sedation team in providing quality care to children and supplies valuable information on the quality of the pediatric sedation technique(s) employed.

What then about the "hardware"? This includes disposables, drugs, and equipment. The mobile kit must have the following contents:

- "Hardware" critical for all procedures
- "Hardware" that will be used for some cases only
- "Hardware" used only occasionally
- "Hardware" that one hopefully will never need to use

The above is crucial for the mobile sedationist. A basic guiding principle is the assumption that the office/facility will provide only suction and light. Pack all the hardware personally, placing it in such a way that it can easily be accessed if needed. Bring even the hardware for which there is only a remote chance of need. Always have more hardware available than you think you might need in order to ensure that you never run out of anything. Check the contents of the mobile kit regularly.

What hardware does the mobile sedationist need in the developing world? It is routine to carry a stethoscope (preferably a precordial stethoscope), blood pressure monitor, and pulse oximeter. Mobile sedationists are encouraged to use an ECG monitor and capnography when deep sedation is intended and to carry a spare pulse oximeter. A thermometer is also advisable, especially as children often present with a runny nose for which an infectious process must be ruled out. It is also advisable to carry a glucometer. The mobile kit should also include items that will improve patient comfort and safety, i.e., a blanket to keep the child warm, a cushion to put behind the shoulders to extend the neck, butterfly sponges to protect the airway from water in pediatric dental cases, and a radio with earphones to play music for the older child.

The kit must also contain items for when complications may arise i.e., oxygen, nasal cannulae, a bag-valve-mask device with reservoir (Ambu-bag®) and airways (nasal and oral) of all sizes. Items that may be needed when disaster strikes must be in the kit and these include a pediatric laryngoscope/blades, a suction, endo/nasotracheal tubes, laryngeal mask airway, a Magil's forceps, resuscitation medications, and a defibrillator.

Mobile sedationists usually operate in the private healthcare environment where the patients are responsible for the expenses and most carry medical insurance.

Management of the Child

Probably the single most important aspect of any successful sedation is to gain the child's trust. Earning a child's trust is not always easy, particularly if there have been past traumatic experiences with general anesthesia or sedation. All sedation techniques must include behavioral management strategies, empathy, understanding, and a patient approach. The protocol for successful behavior management must incorporate two strategies: how to "read the mind" of the child [14] and how to use the specific practical guidelines.

When trying to "read the mind" of the child, it is vital to try and establish a good personal relationship in order to gain their trust. This means that you have to place yourself in the child's shoes and establish rapport. Five important points to remember when interacting with a child are imagine yourself to be the same age as the child you are dealing with; use words that children can understand; try not to lie to the child (this does not mean that one needs to disclose all details); offer encouragement by telling him/her that he/she is good and brave to ensure that the child feels proud; and use information you get from the child to play mind games [14]. Always speak to children slowly/gently and talk to them about nice things, i.e., the smell of their favorite food, the ocean, etc. A child who does not want to make eye contact is not interested in what you are saying and will ignore attempts to establish rapport. Such children are difficult to sedate and may need a different approach and deeper levels of sedation.

How then do we establish rapport with a child? The following practical hints may be useful:

- The office, where procedures are to be performed, is a threatening environment for most children. Communication should not take place in the operating room but in a friendlier environment where the child can be made comfortable. He/she should be encouraged to ask questions and his/her consent should be obtained for the proposed sedation where possible.
- Wear casual, nonoperating room clothing – appearing too formal may create anxiety in children.
- What you say is less important than the way in which you say it. The attitude of the sedation practitioner is an important determinant of success. It is essential that the sedation practitioner shows confidence in what he/she is doing. The child and parent must be confident that the sedation provider knows exactly what is to be done, has the necessary experience, and can deliver safely on the promises. One should never afford the child or parent the opportunity to doubt one's professional ability. Always have a positive attitude that, at times, may be quite difficult. Show the child that you are enthusiastic about what you do and that you are excited to be in a position to be able to help. Confidence in one's own success as sedationist may convince the child that, even though his anxiety is valid, together the two of you can be successful. Never direct your conversation at the parent/escort, always involve the child irrespective of age. Always establish and maintain eye contact with the child – this simple gesture shows the child that you really care.
- Try to find an "ice-breaker" when first meeting the child by making a friendly nonthreatening statement to start the conversation – this may be all that is needed to settle the child down. It is always good to find out about the interests of the child.

- Never look down at the child – if the child is seated or lying down, sit down beside him. It may even be advisable to sit on your haunches in front of the child. That way, your eyes are at the same level and it makes it much easier for the child to relate to the sedation practitioner.
- It is crucial that children never to be crowded – they need their personal space to feel respected.
- It is always wise to tell the child that you need his/her help and that sedation means a team effort. Children are very susceptible to suggestion. Something like, "I cannot do this without your help" will go a long way toward making the child comfortable.

A final question: do cultural factors play a role in the outcome, success rate, and/or achievability of multidrug sedation in children over the age of 5 years? A study of 354 children from eight different cultural groups showed that cultural factors do not influence the outcome, success, or achievability of multidrug sedation in children. The study, however, validated the importance of pre-operative assessment and the use of behavior management techniques [15].

Common Sedation Strategies in the Developing Nations

Oral Route: Single Agent

It is not routine practice to administer oral sedatives for surgical procedures. Children vary in their behavior patterns and it is therefore essential to do a behavioral assessment prior to the procedure. It is good practice to discuss this with the parent/guardian before sedation, as they usually can give the sedation practitioner guidance whether the child needs an oral sedative before surgery. Some children are, however, just too frightened due to previous traumatic experiences, and may thus need a sedative.

Chloral hydrate is a sedative hypnotic still being used in some hospitals for sedation for children under the age of 3 years, especially for painless imaging [16]. The drug has no analgesic activities and the usual dose is 20–75 mg/kg, given orally.

Midazolam is a short-acting, water-soluble benzodiazepine with no analgesic properties. It is the most commonly used benzodiazepine for pediatric sedation and can be administered via various routes. The oral dose is 0.35 mg/kg, 20–30 min before surgery [17]. To make it easier to remember, we advise sedation providers to administer 7.5 mg orally to those children above 8 years of age, and 5 mg to those less than 8 years of age. The child must be constantly supervised and monitored after administration of the oral sedative. The consumption of oral sedatives prior to arriving at the hospital is not permitted. Midazolam is not available in a syrup formulation in Africa, so instead the tablet is crushed and diluted with paracetamol syrup. Alternatively, the aqueous formulation for intravenous midazolam is orally. Midazolam is a useful sedative to combine with other oral drugs.

Oral ketamine provides excellent sedation, analgesia, and amnesia and can be used for painful procedures. In the developing nations, it is seldom used alone and is usually combined with midazolam. Oral ketamine is useful for burn debridement in children at a dose of 10 mg/kg, especially in rural settings because of its excellent safety profile [18]. Acceptable sedation for dental procedures was achieved in children, 2–7 years of age, by the use of 12.5 mg/kg oral ketamine. The incidence of hallucinations was 16.6%, but none were severe [19].

Nasal Route: Single Agent

Intranasal *midazolam* may be uncomfortable for children because it can produce a burning sensation, which may increase anxiety. It is, however, useful in children who refuse to take medication by mouth and for the mentally handicapped. Although a tuberculin syringe can be used to administer 0.2 mg/kg midazolam intranasally, a mucosal atomization device (MAD®) is currently available. This device has a nozzle attached to a syringe and makes nasal administration much easier.

Rectal Route: Single Agent

Rectal administration of *midazolam* is a useful route for providing sedation for younger children. Acceptance is usually very good in small children. The administration of midazolam by this route is especially indicated where children refuse to take oral drugs, are nauseous, vomiting, or very anxious. It can be used alone for painless procedures or in combination with other drugs when analgesia is regular. In one study, rectal midazolam was administered at 1 mg/kg to children 30 min before dental surgery [20]. Satisfactory sedation and recovery outcomes were achieved.

Rectal *diazepam* is a useful and cost-effective alternative sedative for midazolam, especially in rural areas, where the latter drug is often not available. Rectal diazepam, at a dose of 0.70 mg/kg, provides acceptable levels of sedation, and patient acceptance, when administered 30 min before a procedure [20]. Rectal *ketamine* at a dose of 5 mg/kg is also a useful alternative for pediatric sedation [21].

Oral Route: Sedative and Analgesic Combination

The mere fact that no single sedative drug has achieved universal acceptance suggests that each agent has its disadvantages. There is no single oral drug available that meets all the requirements of an ideal drug. Drug combinations are therefore a useful alternative for the management of uncooperative children. A combination of midazolam with ketamine is useful for sedation for short, painful procedures. In a sedation study using oral midazolam at 0.35 mg/kg and oral ketamine at 5 mg/kg, in children 2–7 years of age, the results showed that the combination is a safe, effective, and practical approach to managing children for minor oral surgical procedures under local anesthesia [22]. When oral ketamine and midazolam are used, followed by an intravenous technique, a smaller dose of oral ketamine is advised (2 mg/kg). The latter oral dose of ketamine can also be used in children under the age of 2 years [23] but children must be monitored carefully.

The safe and effective management of children for painful procedures outside the operating room remains a challenge. Dental procedures are common pediatric day-case procedures and are one of the standard and practical research models used for studying the efficacy of minor analgesic agents [24]. The severity of the postoperative pain is related to the number of teeth extracted, and by studying children after six or more extractions an effective clinical research model was established [25]. In addition, this study gave valuable information regarding pain after pediatric dentistry. Children, aged 4–7 years, undergoing dental extractions of six or more teeth, received either tramadol (Tramal®) drops at 1.5 mg/kg or placebo, 30 min before surgery. Both groups received oral midazolam at 0.5 mg/kg (max 7.5 mg) 30 min before surgery. Postoperative rescue analgesia was administered to 19.4% of the tramadol group, compared with 82.8% of the placebo group [25]. This approach showed the value of using effective analgesic drugs, before sedation, for minimizing postoperative pain in children. Pharmacokinetic studies showed that postoperative analgesia lasts for up to 9 h following administration of oral tramadol [26]. In another study, the experimental group of children received tramadol drops 3 mg/kg with oral midazolam at 0.5 mg/kg (maximum 7.5 mg); the control group received only oral midazolam at 0.5 mg/kg (maximum 7.5 mg) [27]. These results showed the analgesic effects of tramadol, its lack of respiratory depression in children, and normal recovery times when used in combination with a sedative. The combination of oral tramadol 1.5–3 mg/kg with midazolam is therefore a useful combination for sedation and pain control for children undergoing painful procedures outside the operating room.

Another useful oral combination of trimeprazine, at 6 mg/ml, and physeptone linctus, at 0.4 mg/ml, in a syrup base [19, 22], can be used for sedation for smaller, painful surgical procedures where a local anesthetic is to be used. It is also a

useful sedative combination for painless procedures as profound sedation is achieved. The usual oral dose is 0.5 ml/kg of the mixture up to a maximum of 10 ml. Unfortunately, the physeptone, an opioid, has a long elimination half-life and is not used as a first-line analgesic. In addition, trimeprazine (3 mg/kg), a phenothiazine derivative, is known to produce a prolonged hangover effect and thus does not make it the ideal combination drug. However, despite these limitations, the low cost makes this combination useful for oral pediatric sedation especially in rural areas. Deeper levels of sedation can be obtained by adding 0.1 mg/kg droperidol to the mixture.

Nasal Route: Drug Combinations

The intranasal administration of drugs for sedation and pain control has some promising features, especially in preschool children with fear of separation from parents and unfamiliar surroundings. Intranasal sufentanil (1.5–3 μg/kg) has been found to facilitate separation of children from parents and can provide postoperative analgesia [28]. In another research study, children aged 5–7 years, weighing 15–20 kg, and having 6 or more teeth removed were studied [29]. The combination of intranasal sufentanil and midazolam was compared with intranasal ketamine and midazolam for sedation and postoperative analgesia. Children in the sufentanil group received 1 μg/kg of sufentanil and 0.3 mg/kg of midazolam 20 min before induction of anesthesia. In the ketamine group, children received ketamine 5 mg/kg and midazolam 0.3 mg/kg intranasally. The study demonstrated the safety and efficacy of both methods. Key features were the ease of administration combined with rapid onset of action. Both groups were equally sedated. Effective postoperative analgesia for multiple dental extractions were provided in the sufentanil group and 72% of children did not need rescue analgesia, compared to 52% in the ketamine group. These combinations have promising features and could be used as sole agents for sedation and analgesia, but also in combination with intravenous drugs.

Multimodal Routes: Drug Combinations

The use of parental drug combinations is often necessary in Africa, particularly for dental procedures on the many with poor hygiene. Multiple extractions and fillings in dentistry are commonplace and the waiting lists for general anesthesia are extremely long. The need for alternative treatment options encourages the development of multidrug sedative plans.

Multimodal Analgesia with Opioids

Commonly, multimodal therapy begins with a benzodiazepine for anxiolysis. Midazolam is administered –by oral, nasal, intravenous, or rectal route. This is then followed by the use of one of the ultra–short-acting opioids [30, 31], the phenylpiperidines, which are generally the drugs of choice. Alfentanil and sufentanil are used either for bolus administration or as part of an infusion technique. A research study on 270 children (<8 years age) was designed to establish the safe bolus dosages and infusion rates of alfentanil when combined with propofol, ketamine, and alfentanil [32]. It was concluded that, with stable vital signs and no respiratory depression, an intravenous bolus dose of 1–2 μg/kg alfentanil, titrated, would be safe and effective in children. As a bolus dose, alfentanil should be given 2 min before the expected painful stimulus. As an intravenous infusion, and in combination with other drugs, a dose of 10–12 μg/kg/h alfentanil is advisable.

Remifentanil is also available and has been used for children preferably in a sedation unit within hospital. The author has administered remifentanil to 154 children, aged 3–10 years, as a 0.05 mg/kg/h infusion for dental procedures. In a separate another 20 ml syringe, 200 mg of propofol is mixed with 20 mg of ketamine and titrated to effect. In our experience, a drop in oxygen saturation levels of <92% occurred in 9% of children. In children under the age of 5 years, desaturation occurred in 17%, coincident with flexion of the head, depression of the chin by the dentist, or excessive water in the mouth – all preventable. Flexion of the head caused desaturation

in 3% of children (5–8 years age). In children >8 years of age, there were no incidences of desaturation <92%. Remifentanil has also been used for analgesia for dermatology cases and laser treatments of the face, situations that do not permit injection of local anesthetic.

Intravenous ketamine (0.1–0.5 mg/kg titrated) remains a valuable drug in the practice of polypharmacy because of its unique sedative/analgesic/amnestic properties. For short procedures, 50 mg ketamine is mixed with 90 mg propofol in a 10-ml syringe. The desired intravenous sedative dose is then titrated as necessary up to a maximum of 0.3 mg/kg of ketamine, which gives a maximum dose of 0.5 mg/kg of propofol.

Multimodal Analgesia Without Opioids

The use of nonopioid analgesic combinations helps to relieve and attenuate discomfort following painful procedures. Nonsteroidal anti-inflammatory drugs, alpha-2 agonists, paracetamol, and ketamine can all provide beneficial analgesic effects when administered as part of a multimodal sedation regimen. For painful procedures, an intravenous infusion of 15 mg/kg paracetamol over 20 min is initiated 30 min before the procedure. Immediately before the procedure, ketorolac is administered at a bolus dose of 0.5 mg/kg intravenously. For longer procedures, ketorolac can be administered as an infusion of 0.17 mg/kg/h and supplemented with 0.5 mg/kg ketamine as needed [33]. Propofol is another option, administered as bolus or infusion.

In conclusion, the approach to pediatric sedation in underdeveloped countries is based on the concept of multimodal pain management [34]. For potential painful procedures done under sedation outside the operating room, an aggressive peri-operative analgesic and sedative approach that will provide effective analgesia, patient comfort, sedation, minimal side-effects, and safety are needed. In addition, postoperative analgesia is crucial. This can be achieved by using two treatment options, i.e., multimodal analgesia without opioids or multimodal analgesia with the opioids. Opioids, used with discretion, play a crucial role in polypharmacy for painful procedures. It is anticipated that nonopioid analgesic drugs will assume a future key role as analgesics during procedural sedation outside the operating room.

Case Studies*

Summary of the Three Case Presentations

Case 1: A magnetic resonance imaging (MRI) brain scan of a 22-month-old child, with a slight cough following an afebrile grand mal seizure 12 h earlier.

Case 2: A 2-year-old boy with cystic fibrosis requiring an endoscopic retrograde cholangiopancreatography (ERCP).

Case 3: A 2-year-old girl requiring a vesiculo-cysto-urethrogram (VCU) for recurrent urinary tract infections.

* These case studies are examples of didactic and practical material, which is Postgraduate Sedation Diploma Course.

Case 1

A 22-month-old boy was referred to the radiology department for an MRI brain scan following on an afebrile grand mal seizure 12 h earlier. On examination, the child presented with a slight cough but otherwise appeared to be in good health. As the exact cause of the grand mal seizure was not known, all possible causes had to be kept in mind and the effect of the sedation on the intracranial pressure and the respiratory system had to be as minimal as possible. The following salient points, as applicable to this case, and as taught in the Postgraduate Diploma in Sedation Course:

- Merely supplementing oxygenation with oxygen using nasal prongs does not necessarily

mean that your child is breathing adequately, and not becoming hypercarbic. An unobstructed airway without drugs that will depress respiration is mandatory.

- The injected intravenous drugs work on "the organ under examination"! Unseen changes in cerebral blood flow and activity may occur with the drugs administered.
- Concomitant drugs (especially anticonvulsants) that could interact with the sedation should be carefully considered. Generally, prescribed medication must be given as usual.
- Copious notes on the pre-sedation mental condition of the child are essential to avoid later questions on the possible effect of the sedation on pre-existing pathology.
- A partially obstructed airway and labored breathing will not necessarily cause significant desaturation. This may be difficult to evaluate since the child will be lying inside the tube of the MRI apparatus and be largely out of sight.
- Many children of this age have enlarged tonsils or adenoids and may be obligate mouth breathers. Allergic rhinitis is also extremely common and the mother should be able to inform you if the toddler snores at night!
- A rolled-up towel or sponge wedge should be inserted under the shoulders of the child. This stabilizes and extends the head to prevent possible airway obstruction. Soft comfortable MRI compatible sponges can be used as wedges between the head and ears and the cradle. These wedges help to block out the noise of the MRI.
- A fiber optic pulse oxymetry probe, correctly attached to one of the fingers/toes, is absolutely essential. Capnography will be of great value if available.
- Because the temperature in MRI rooms needs to be kept low, a blanket should be used to cover the exposed skin to prevent hypothermia, and to tuck in the arms as snugly as possible.
- As a distance of 4 or 5 m away from the sedated child may need to be maintained, it may be necessary to connect two or three extension sets in order to administer the intravenous drugs.
- Extreme caution should be exercised with devices such as infusion pumps as these devices, if placed close to the coil, may be attracted by the magnetic field and may fly into the tunnel and inflict possible fatal injury to the child.
- The radiologist may request the administration of an intravenous contrast agent. The agent must be administered at the level of the cannula inserted into the vein. If the drug is administered via existing extension sets, this may result in the inadvertent administration of a further bolus of the sedation combination.

Case 2

A 2-year-old child with cystic fibrosis was referred by the gastroenterology department of the local academic hospital for endoscopic retrograde cholangiopancreatography (ERCP).

After induction of sedation, the gastroenterologist will need to turn the child onto his/her abdomen because a C-arm X-ray unit is employed to capture images of biliary tract filling with contrast medium, once the Ampulla of Vater had been cannulised by the endoscopist. A dedicated nursing professional is positioned at the head end of the table for the entire procedure to monitor the patient, to keep the airway clear of secretions, and position the head to maximize patency of the airway. Once the fiber optic scope enters into the second part of the duodenum, the stimulus in the pharynx is largely over and the maintenance of sedation, with i.e., a propofol infusion, is reduced to the lowest dose necessary to keep the child cooperative. Because the procedure subsequently can become painful, due to an obstruction needing a sphincterotomy and a stent, 0.2–0.3 mg/kg of incremental intravenous ketamine can be administered – this

should provide sufficient analgesia. In this case, a small dose of an opioid e.g., alfentanil can also be used.

Salient points for consideration in complicated cases like these include

- The sedationist should remain acutely aware of the respiratory depressant effect of propofol and the opioids. Due to the fact that the child is lying on his stomach during this procedure, respiration is already depressed and care should be taken to use doses of these drugs that will not depress respiration even further – titration of drugs is important. Positioning of the child is crucial.
- An ERCP under sedation should only be done by a skilled gastro-enterologist who is fully conversant with ERCP. This is clearly not an occasion to teach the procedure. On the other hand, the sedation provider should also have a good understanding of the technique in order to preempt possible sedation complications that may arise. Thus, a good team of skilled operator and skilled sedationist will help to reduce the inherent risks and the concomitant stress.
- At times, parents may be invited to be present during an examination; however, in this particular instance, it is wise to exclude them. The presence of noncontributing members to the procedure is a distraction from the undivided attention one must give to the child in such a complicated case.
- Cases like these may go on for longer than an hour and, as in the case of general anesthesia, co-morbidity increases proportional to the length of time of sedation. Thus, careful planning is essential.
- Continuous oxygen administration at high flow rates, through nasal prongs, is mandatory throughout procedures of this nature.
- Capnography is very useful in cases like this.

Case 3

A 2-year-old girl with recurrent urinary tract infections was referred by her urologist for a vesiculo-cysto-urethrogram (VCUG). The important teaching points from this scenario, as emphasized in the Postgraduate Sedation Diploma Course, include

- VCUGs are seldom urgent and it is preferable to optimize the preparation of the patient prior to the procedure.
- Urogenital abnormalities may be part of a broader syndrome and therefore possible impaired renal function must be kept in mind as it may affect the action of the drugs administered.
- Hypothermia is possible in cases like these due to the low ambient temperatures of an air-conditioned X-ray suite with a hard noninsulated X-ray table and the exposure of the lower abdomen, perineum, and legs of the patient. The child can be placed on an insulated table with a linen saver and plastic space blanket to prevent unnecessary heat loss during the procedure (plastic space blankets do not interfere with X-rays).
- X-rays are taken at intervals while the radio-opaque contrast material is filling the bladder. Contrast media are iodine based and an allergic reaction is possible. Therefore, induction with an antihistamine is recommended.
- Supplemental analgesia is required at the painful stages of the procedure, especially during urethral catheterization. It is therefore advisable to have this event follow closely on the induction phase of the sedation.
- Another uncomfortable phase in the procedure may occur when the radiologist applies pressure to the full bladder to elicit reflux to the ureters.
- It is advisable to avoid high doses of glycopyrrolate or atropine and an antihistamine, as these anticholinergic agents may inhibit spontaneous micturation and the evaluation of reflux once the bladder is full.
- Because X-ray exposure is a short event, the patient only requires to be immobilized for a few seconds at a time. The level of sedation therefore need not be as deep as for intensely painful procedures. The presence of the sedationist in the x-ray suite, at

the head of the patient, will help to ensure that an open airway is maintained throughout the procedure.
- Do not remove the intravenous infusion prematurely as the radiologist may decide, at the end of the procedure, to continue with an intravenous pyelogram and this may require sedation for a further 20 min or more. If the intravenous line was removed prematurely, it will mean that it needs to be re-established.

Special Considerations for All Cases

- The facility being used for procedural sedation outside the operating room should always meet all the criteria for safe sedation practice. The mobile sedationist must ensure the availability of all the anesthetic and emergency equipment that may be required. In addition, a registered nursing professional with pediatric life support certification must be in attendance.
- The patient must be optimally prepared for the procedure. This includes a pre-sedation assessment, pre- and postsedation instructions, nil per mouth guidelines, and informed consent. In addition, ensure that the patient fully understands what sedation entails and is fully informed and understands the pre-sedation and postsedation instructions.
- When using an intravenous technique, a local anesthetic skin patch (EMLA®) with a pictorial description of how to apply it to the child's hand, foot, or cubital fossa should be considered. Sometimes, the anesthetic patch may be positioned in the wrong place or be on for too short a period of time, this may create additional challenges.
- An oral sedative, if administered, may not be very effective in reducing anxiety, and the child can still be very anxious. Consider the use of rectal midazolam in young children.
- A very anxious or fearful child needs a sympathetic approach. However, despite the sedationist's best efforts, some children may simply be beyond pacifying due to negativity and resistance – not uncommon in children.
- Despite one's best efforts, one may be unsuccessful in cannulating the vein and end up with the cannula being subcutaneous. Ketamine does sting when given subcutaneously, but can be mixed with a small dose of lignocaine and given very slowly subcutaneously, through the intravenous cannula. This represents an escape route to sedate the child in a sticky situation.

Recommended Management Techniques

- There is no one-size-fits-all drug, as some procedures may require more sedation, while others require more analgesia. Painful procedures need a combination of both. It helps to simplify matters and reduce variables if one uses a routine drug combination that suits most situations. The following combination drugs serve our purposes of a "standard combination" for most procedures very well – midazolam, ketamine, propofol, mepyramine maleate (an antihistamine), the nonsteroidal anti-inflammatory agents, and the opioids. How can we combine some of these drugs that can be used for the above cases?
- Select a 10-ml disposable syringe that can be filled to 12 ml. Draw up 1 ml of ketamine 100 mg/ml and add mepyramine maleate (an antihistamine) 50 mg/2 ml, into the 10-ml syringe with 100 mg ketamine, to make up 3 ml. Lignocaine 1% (10 mg/ml) is added to the ketamine/mepyramine mixture. This is to reduce pain on injection of the subsequent drug, propofol. Fill up the balance of the syringe with propofol 1% to 12 ml. The above mixture forms the basis of our sedation drug combination – other agents i.e., analgesic and anticholinergic drugs can additionally be administered if indicated. Intravenous ketorolac 0.5 mg/kg, administered intravenously, is a very useful analgesic drug in children.
- With intravenous administration of drugs in children, one needs to titrate to effect.

Rules are difficult as body mass index, volume of distribution, metabolism, age, and concomitant pathology all have a profound effect on the response. This is where the experience and hard-earned training of the sedationist comes to the fore.

- Proceed with the slow administration of 1–2 ml of the combination and observe how quickly the child responds, and the depth of sedation achieved. Be sure to give the child at least 2 min in which to respond to the combination administered.
- If the child is not settling down, two options are possible: administer another 1 or 2 ml of the combination, even more slowly this time. Consider converting to plain propofol with residual ketamine working in the background. If the child is nicely sedated with eyes closed, but you know that your next step of the procedure is going to be especially painful, then administer a bolus of 1 ml of the ketamine/propofol combination slowly and give 30 s for this to take effect.
- A maintenance dose of the combination of between 2 and 8 ml per hour may be required to keep the child sedated. Expect to discard more than half of the combination for cases lasting less than 2 h.
- If a dose of the combination of 1 ml per year of age is not settling down the child, consider adding another synergistic drug.
- Always remember, sedation makes many procedures possible but the depth of sedation is directly proportional to the risk profile. Never take your mind off the risk you are generating in proportion to the therapeutic value of your intervention. There is a cut-off point. It is not the intention to duplicate the general anesthetic theater environment. Thus, be fully aware that if the procedure becomes surgically complicated, it may require that the child be done under general anesthesia. Do not be tempted to push the envelope and find yourself outside your comfort zone. It is the safety of the child that should be the main concern and not the convenience of the surgeon.

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Part III

Safety in Sedation

Pediatric Sedatives and the Food and Drug Administration: Challenges, Limitations, and Drugs in Development

19

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Introduction

In order for new medications to be marketed in the United States, they must be approved under the Food, Drug, and Cosmetic (FD&C) Act. The Food and Drug Administration (FDA) approves products based on an independent review of evidence obtained from chemistry and manufacturing data, toxicology and pharmacology studies, and clinical trials. Sponsors submit data for approval of a drug to the FDA in a New Drug Application (NDA), or biologic in a Biologic Licensing Application (BLA). During the review of the NDA or BLA, FDA assesses if the product works in a specific population to treat a specific condition (efficacy) and to assess the adverse events that occur with the use of a given product (safety). Approval of an NDA or BLA in the United States depends on an analysis that the benefit from the product outweighs the risk of adverse events associated with its use.

Imaging, invasive diagnostics, and minor surgical procedures on pediatric patients outside the operating room setting have increased, and there is a need for sedatives that have been properly assessed in the pediatric population for this indication. This chapter will review the process of obtaining FDA approval for a drug or biologic with a focus on sedation.

General Drug Development

Under current U.S. regulations, any use of a drug or biologic not previously approved for marketing requires submission of an Investigational New Drug application (IND) to the FDA. The data gathered during the IND phase (chemical analyses, animal studies, and human clinical trials) become part of the NDA. The development of a medication for sedation is a stepwise process involving an evaluation of chemistry, preclinical, and clinical information. While pediatric studies may begin during the IND phase for some products, for most products, it is likely that most of the clinical trials would begin after the adult development is complete (Fig. 19.1).

Initial studies in humans (Phase 1 trials) are the first stage of testing in human subjects. Normally, a small number (i.e., 20–50 people) of

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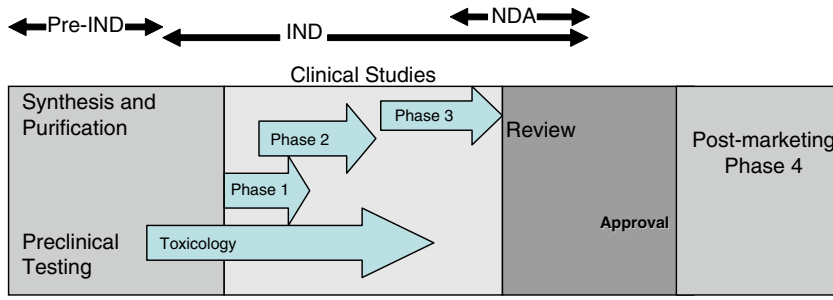

Fig. 19.1 Drug development

healthy adult volunteers will be tested in trials designed to assess the first time use in human for safety, tolerability, proof of concept for efficacy, and pharmacokinetics.

Pharmacokinetics (pk) are often assessed in Phase 2 studies. PK studies provide information on the way a drug is handled by the body, and includes measures such as area under the curve (AUC) and maximum concentration (Cmax). There are also pk parameters calculated from these measures such as clearance, half-life and volume of distribution reflect the absorption (A), distribution (D), metabolism (M), and elimination (E). The overall process (ADME) ultimately controls the degree of systemic exposure to a drug and its metabolites after administration. The pharmacokinetic parameters must be considered when establishing the appropriate dose of a drug.

Once the first human exposure has been completed, and some pk parameters assessed, additional studies (Phase 2 studies) are performed on a larger number of participants (i.e., 20–300 patients) to assess the treatment effect size, provide safety assessments, and test the response to different doses in a larger group of volunteers and patients. The information obtained from Phase 2 studies is critical in designing the definitive Phase 3 studies.

The Phase 3 studies should leverage the data from all other preclinical and clinical studies to determine a dose, and to calculate the number of patients required to demonstrate efficacy based on the treatment effect, and specific safety signals that will need to be assessed. These studies are adequately controlled powered studies designed to demonstrate both safety and efficacy.

A NDA is submitted to the FDA once all studies have been completed to support a new pharmaceutical for sale and marketing. A supplemental NDA (sNDA) may be submitted if the industry seeks to change the indication or population for a pharmaceutical product that has already been approved. The NDA (or sNDA) contains all information necessary to market the product including:

- A technical description of methods used in manufacturing (Good Manufacturing Practice, GMP), and data on the drug's quality (supporting the drug's identity, strength, stability, and purity)
- Complete data from preclinical and clinical studies to support the safety and effectiveness of the drug in its proposed use(s).
- The drug's proposed labeling (package insert).

The product labeling describes the conditions of study, to include the patient population studied, the doses used, and the endpoints assessed. Use of the product under the specific conditions described in the product label is known as "on label use." Use of the product outside of these parameters (condition/disease studied, population studied, dosage regimen used, etc.) is known as "off label" use.

Pediatric Legislation

Historically, many pharmaceuticals, including those used in sedation, were not studied in pediatrics, and thus, the majority of pediatric practice was "off label." Approximately 75% of medicines used in children did not have prescribing information on how to use the medicines specifically in

children prior to legislation encouraging and requiring the study of medication in the pediatric population [1]. While the number of drug labels with pediatric information has improved under this process, the majority of commonly used sedatives do not have pediatric labeling or lack robust data (Table 19.1).

Prior to the passage of important pediatric legislation, many pharmaceutical manufacturers were reluctant to study drugs in children due to ethical and financial constraints or trial design challenges [2]. The pediatric population accounts for 25% of the U.S. population and represents a special population that must be addressed during product development [3].

Because of the historic lack of data from adequate clinical trials, medication was often administered to children empirically, assuming that they were "little adults." This assumption resulted in dosing based on the adult dose being fractionated to the child's weight rather than based on intrinsic factors due to differences in growth and development (e.g., volume of distribution and maturation of metabolic pathways). Safety and efficacy were always assumed to be the same in the pediatric and the adult population without taking into account the safety and efficacy differences that can be seen in a growing and developing pediatric patient.

The Food and Drug Modernization Act of 1997 (FDAMA) created an incentive program known as pediatric exclusivity. This provision allowed the FDA to issue a formal request, known as a Written Request, outlining the studies needed on a specific drug for one or more conditions or indications. The Written Request includes details of study design, number of patients needed, and important safety and efficacy endpoints to be measured. The Written Request also includes a due date for submission of the study data to the FDA. The FDA can grant 6 months of marketing exclusivity to sponsors who complete the voluntary pediatric studies using good scientific principles, blocking the approval of generics for the entire product line and all indications already approved, resulting in financial return for the sponsor who performed the studies [4]. Although FDAMA sunset on 1 Jan 2002, the incentive was reauthorized by the Best Pharmaceuticals for Children Act of 2002 and again in 2007. The exclusivity was extended to biologic products under the Patient Protection and Affordable Care Act of 2010.

There is also an important section of BPCA to address off patent therapeutics where the exclusivity provision provides no incentive to sponsors to study the drug, and Written Requests for which there is patent and the sponsor has declined to study the product as outlined in the Written Request. This section of BPCA allows for the FDA to issue a Written Request first to the application holder(s), and then, if declined, forward it on to the National Institutes of Health (NIH), National Institute of Child Health and Human Development (NICHD).

Under these programs, almost one-third of the products studied had new, pediatric specific safety information included in labeling. Among those safety findings were rare cases of seizures reported in pediatric patients in association with sevoflurane use for induction/maintenance of general anesthesia. Most cases were in children and young adults, most of whom had no medical history of seizures [5].

The Pediatric Research Equity Act (PREA), first enacted in 2003, requires pediatric assessments of new drugs and biologics for all new active ingredients, indications, dosage forms, dosing regimens, and routes of administration. The pediatric assessment is data adequate to assess the safety and effectiveness and support dosing of the product for the claimed indications in all relevant pediatric subpopulations. PREA works in conjunction with BPCA but unlike BPCA, PREA applies only to those drugs and biologics developed for diseases and/or conditions that occur in both the adult and pediatric populations. Drugs with Orphan indications are exempt from PREA. Both BPCA and PREA were reauthorized under the Food and Drug Administration Amendment Act of 2007.

The pediatric legislation has generated almost 400 product labels (1997–2010).

Pediatric studies resulted in an approved pediatric sedation indication for midazolam, and an induction and/or maintenance of anesthesia indication for propofol. Other Written Requests for

Table 19.1 Commonly used drugs for sedation in the pediatric population

Agent	Approved indication Based on most recent label as of September 2010	Pediatric information
Chloral hydratea	Safety and efficacy not established in children	Drug not approved by FDA
Dexmedetomidine	Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting Sedation of nonintubated patients prior to and/or during surgical and other procedures	Pediatric Use: The efficacy, safety, and pharmacokinetics in patients less than 18 years of age have not been established. Therefore, this product should not be used in this population
Diazepam	Relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff-man syndrome; and tetanus Adjunct in status epilepticus and severe recurrent convulsive seizures	Although anxiolytic indication appears in labeling for adults, pediatric approval limited to use in tetanus and status epilepticus and recurrent convulsive seizures Not approved below 30 days of life
Etomidate	Etomidate is a hypnotic drug without analgesic activity	There are inadequate data to make dosage recommendations for induction of anesthesia in patients below the age of ten (10) years; therefore, such use is not recommended
Fos propofol	Fospropofol is a sedative-hypnotic agent indicated for the monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures	Safety and effectiveness in pediatric patients have not been established because fospropofol has not been studied in patients <18 years of age. Fospropofol is not recommended for use in this population
Ketamine	Sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation Induction of anesthesia prior to the administration of other general anesthetic agents To supplement low-potency agents, such as nitrous oxid	Safety and effectiveness in pediatric patients below the age of 16 have not been established
Lorazepam	Treatment of status epilepticus In adult patients for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and a decreased ability to recall events related. To the day of surgery	Pediatric pharmacokinetic data included in labeling No pediatric dosing included in labeling There are insufficient data to support the efficacy of injectable lorazepam as a preanesthetic agent in patients less than 18 years of age Information in labeling about the “gasping syndrome” associated with benzyl alcohol, polyethylene glycol, and propylene glycol, components of lorazepam injection

Methohexital	In adults as follows: IV induction of anesthesia prior to the use of other general anesthetic agents IV induction of anesthesia and as an adjunct to subpotent inhalational anesthetic agents for short surgical procedures Along with other parental agents, usually narcotic analgesics, to supplement subpotent anesthetic agents for longer surgical procedures IV anesthesia for short surgical, diagnostic, or therapeutic procedures associated with painful stimuli As an agent for inducing a hypnotic state	Methohexital can be used in *pediatric patients older than 1 month* as follows: For rectal or IM induction of anesthesia prior to the use of other general anesthetic agents For rectal or IM induction of anesthesia and as an adjunct to subpotent inhalational anesthetic agents for short surgical procedures The safety and effectiveness of methohexital in pediatric patients below the age of 1 month have not been established. Studies of methohexital intravenously in pediatric patients have been reported in the published literature. The literature is not adequate to establish the safety and effectiveness in pediatric patients Pediatric dosing information is included in labeling
Midazolam	IM or IV for preoperative sedation/anxiolysis/amnesia; IV as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations, and other procedures either alone or in combination with other CNS depressants IV for induction of general anesthesia, before administration of other anesthetic agents IV midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia); Continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting	The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients
Pentobarbital	Sedatives Hypnotics, for the short-term treatment of insomnia, since they appear to lose their effectiveness for sleep induction and sleep maintenance after 2 weeks Preanesthetics Anticonvulsant, in anesthetic doses, in the emergency control of certain acute convulsive episodes, e.g., those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics	No adequate well-controlled studies have been conducted in pediatric patients; however, safety and effectiveness of pentobarbital in pediatric patients is supported by numerous studies and case reports cited in the literature The recommended pediatric dosage ranges from 2 to 6 mg/kg as a single IM injection not to exceed 100 mg

(continued)

Table 19.1 (continued)

Agent	Approved indication Based on most recent label as of September 2010	Pediatric information
Thiopental[a]	This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA As the sole anesthetic agent for brief (15 min) procedures Induction of anesthesia prior to administration of other anesthetic agents To supplement regional anesthesia To provide hypnosis during balanced anesthesia with other agents for analgesia or muscle relaxation For the control of convulsive states during or following inhalation anesthesia, local anesthesia, or other causes In neurosurgical patients with increased intracranial pressure, if adequate ventilation is provided For narcoanalysis and narcosynthesis in psychiatric disorders	No pediatric section

[a] Unapproved drugs: background information

The FD and C Act generally requires that drugs marketed in the US be shown to be both safe and effective prior to marketing and widespread use in the general population. The FDA's evidence-based system of drug approval and the OTC monograph system play essential roles in ensuring that drugs are both safe and effective. For a variety of historical reasons, some drugs, mostly older products, continue to be marketed illegally in the United States without required FDA approval

dexmedetomidine and lorazepam have been issued, and studies are pending. Dexmedetomidine has required studies for sedation in pediatric patients as well. Both lorazepam and ketamine have been placed on a priority list by NIH to be studied under BPCA, and lorazepam studies are currently underway. A randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in adolescent patients (12–18 years old) undergoing upper endoscopy and randomized, double-blind, dose-controlled clinical trial in infants and very young children (ages 1 month up to 3 years old) undergoing sedation for procedures such as lumbar puncture and/or MRI is still pending as a PREA study requirement. The studies of the youngest patients will not be conducted until preclinical studies delineating risks of apoptosis are complete.

Drug Development for Pediatrics

Rational drug development depends on a thorough evaluation of the preclinical and adult studies needed prior to initiation of pediatric studies and the trial design that will best support the dosing, safety, and efficacy of the medication in pediatric patients.

The timeframe for consideration of trials in the pediatric population depends on what is known about the compound and the circumstances surrounding clinical use of the product. Planning for pediatric studies should begin early and as soon as there is evidence that the product may provide benefit to the pediatric population. Drug development for the pediatric population requires a unique focus and a full review of the chemistry, manufacturing, preclinical, and clinical data must be performed to assess the potential for effects unique to the pediatric population.

Chemistry and Manufacturing Controls

While most chemistry and manufacturing control issues are resolved once a product has been developed for adults, there are unique aspects for pediatrics that must be addressed. Many medications that are administered via the oral route are marketed initially as tablets or capsules. Not all children are capable of swallowing tablets or capsules, particularly young children or those with developmental delay. Most children 6 years of age and older can swallow tablets or capsules, but even up to 10% of patient ages 6–12 years cannot swallow this dosage form. PREA requires the development of an age-appropriate formulation unless the sponsor can show reasonable attempts to produce a formulation have failed. Examples of age-appropriate formulations include, but are not limited to, oral suspensions and solutions, sprinkles, dissolvable strips, tablets and capsules, and intravenous/intramuscular solutions.

Stratification for a study of an oral agent may involve dividing patients into two groups: those capable of swallowing the tablet or capsule (e.g., patients >6 years of age) and those who cannot.

In addition to the need for development of specific formulations for a given age group, the route of administration may also affect stratification due to dosing issues as well as safety concerns. For example, absorption of oral medications in infants may be unpredictable due erratic and delayed gastric emptying, alkaline gastric pH, and diminished intestinal and biliary secretion [6]. Thus, drugs administered via the oral route may require enrichment of patient enrollment in younger age groups.

Ability to take the medication is important for pediatrics, and so is the availability of a flexible dosage form. Unlike adults, most pediatric patients are dosed on a milligram per kilogram basis, and dosage forms must be flexible. Age-appropriate formulations must take into account the need to adjust the dosage administered. Even formulations that appear ready to use in all populations (intravenous or oral solution) may contain excipients such as benzyl alcohol which can cause gasping syndrome in preterm infants and thus render the product unsafe for use in this population [7].

If it is not possible to develop a commercially marketable formulation, compounding may be an option. A compounded formulation utilizes an

approved and marketed formulation that can be transformed by a licensed pharmacist, in a licensed pharmacy, using commercially available ingredients. Under this circumstance, a sponsor could submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. The following information must be provided and included in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information and bioavailability. A relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

Preclinical Studies

Preclinical studies are required for the approval of all drugs and biologics, however, additional toxicology testing may be needed before proceeding into the pediatric population. The nonclinical safety evaluation of pediatric drugs and biologics should primarily focus on potential effects on growth and development that have not been studied or identified in previous nonclinical and clinical studies. Juvenile animal testing may be useful in assessing potential developmental age-specific toxicities and differences in sensitivity between adult and immature animals.

The known pharmacological and toxicological properties of the drug relative to the proposed patient population should be considered. Juvenile animal studies are especially relevant when known target organ toxicity occurs in adults in tissues that undergo significant postnatal development, such as the nervous system. This is particularly relevant for the sedative class because the mechanism of action results from effects on the central nervous system.

Both rodent and primate studies have demonstrated a potential risk of apoptosis in the developing brain when anesthetics such as ketamine are administered [8–10]. Drugs that act as *N*-methyl-d-aspartate (NMDA) receptor antagonists and those that act in an agonistic manner at the aminobutyric acid (GABA) receptor (a.k.a. GABA-mimetics) induce neuronal injury and death in the brains of juvenile rodents [11]. Drugs that exert their effects at one or both of these receptors include benzodiazepines, and inhaled anesthetics, chloral hydrate, etomidate, propofol, ketamine, and nitrous oxide. While evidence of neuronal susceptibility to neurotoxic insult has come from recent studies, the data also demonstrates a variation of the toxicity based on stage of development, dose, and duration of exposure. While this finding have led to a recommendation to delay surgeries requiring sedation if possible, no real changes in clinical practice have been recommended at this time [12]. The methodologies for assessing this type of toxicity in humans have not been developed, and while concerning, the clinical relevance of these findings in humans remains unknown. It is even more difficult to determine how this data translates into the risk for pediatric patients requiring sedation for a necessary procedure outside of the operating room (e.g., lumbar puncture, bone marrow aspirate, orthopedic intervention, suturing, dental work).

During drug development there is not only a need for the toxicological assessments to focus primarily on the active chemical , but testing the inactive ingredients in the clinical formulation can also be important, particularly when a drug's pharmacodynamics or distribution are altered by the inactive ingredients or when uncharacterized excipients are present.

Clinical Trials

Ultimately, clinical trials must be performed in the pediatric population. The timing of such studies and the types of studies conducted depends on the condition being treated and the knowledge of the drug under study. There are many considerations that must be considered in pediatric clinical trials to include protection of pediatric study participants, determining the correct dose, extrapolation of efficacy, recruitment and retention of an adequate number of patients, and choice of controls.

Ethics

Studies in pediatric patients have specific ethical considerations that must be followed. These principals are described fully in 21CFR part 50, subpart D "Additional Protections for Children Involved as Subjects in Research." Children may be involved in biomedical research only after there is some evidence that the product may provide benefit to the pediatric population, and this should be established in the adult population if possible. Since studies will need to be performed in the pediatric population, there must be the potential for the enrolled child to benefit from the treatment. A minor child cannot legally consent to participate in a study, and this, coupled with the fact that the child must have the potential for direct benefit means that only children with the condition of interest can be enrolled in the clinical trials. This principle holds for pharmacokinetic and pharmacodynamic studies as well as studies assessing safety and efficacy. Studies that can be performed in adults, such as bioavailability studies, can be performed in adults.

Pharmacokinetics and Pharmacodynamics

Pediatric pharmacokinetics can differ from adult pharmacokinetics due to intrinsic factors, such as organ development, body weight, and body surface area. Growth and developmental can also lead to changes in pharmacokinetic parameters. For the pediatric population where growth and development are rapid, adjustment in dose within a single patient over the treatment period may be important to maintain a stable systemic exposure depending on the therapeutic window.

The pediatric population includes a broad range of ages to include newborns and teenagers – two groups that are different in so many ways. The age breakout that is generally recommended is as follows, but may change based on the metabolic pathway of the drug or if there is another scientific reason (Table 19.2).

Table 19.2 Age groups for pediatric studies

Age groups
≥1 month to <6 months
6 months to <2 years
2 years to <6 years
6 years to <12 years
12 years to 18 years

While traditional pk studies in the adult population may require intensive blood sampling, there are times when an alternate approach in pediatrics is required because of their limited blood volume. One strategy for obtaining adequate pk information with fewer blood draws in children is to perform a population pk study rather than a traditional pk study. This approach relies on infrequent (sparse) sampling of blood from a larger population than would be used in a standard pharmacokinetic study. Samples can be collected at various times of day and repeatedly over time in a given subject, estimates of both population and individual means, as well as estimates of intra- and intersubject variability can be obtained if the population pk study is properly designed. A large number of patients are needed, which can be a challenge in some pediatric diseases and conditions, and while adult pk studies can often be performed in healthy volunteers; this is not the case in pediatrics. As stated previously, under most circumstances, only children with the condition of interest can be enrolled in the clinical trials because of special protections afforded to special populations under 21CFR part 50, subpart D.

Pharmacokinetics studies should identify a lowest *effective dose* for the drug (i.e., the lowest dose that demonstrates a statistically significant difference between the to-be-marketed drug and the comparator), and a range of doses that can be used in the pivotal trials. Multiple doses should be evaluated for each age group, for example, the Written Request for rocuronium (for use during anesthesia) required three doses to be studied. The selection of the doses to be used in the pk/pd study can be informed by literature, or current medical practice, and/or dosing in adults.

Pharmacodynamic endpoints should also be measured when collecting blood and/or urine samples to provide some understanding of

concentration-response relationships for both efficacy and toxicity. The term pharmacodynamics, or the response component of the exposure-response measurement, refers to both the desired and the undesired effects that the drug or biological does to the body. When possible, both pk and pd data in pediatric trials should be collected and analyzed to determine how the two are linked, i.e., the pk-pd (or exposure-response) relationship. Age-appropriate sedation scale(s) must be used for Phase 2 and Phase 3 studies. Since the studies will likely be multicenter, the same age-appropriate instruments must be used at each study site.

Although additional validation is needed, several scales may be appropriate for use in nonverbal children, particularly the COMFORT/ COMFORT-behavioral scale and the University of Michigan Sedation Scale (UMSS). The studies supported by the NIH/ NICHD in response to a Written Request issued by the FDA for the use of lorazepam for sedation used the COMFORT scale to measure sedation. An objective measure derived from EEG recordings, the Bispectral Index (BIS) may also be useful for monitoring the depth of sedation. Capnography, along with pulse oximetry, may assist in detecting hypoventilation.

The data from the Phase 2 studies will provide support for dose selection and the statistical plan to adequately power the Phase 3 studies. In addition, it can provide proof of concept and may support extrapolation of efficacy from adequate and well-controlled adult trials.

Extrapolation

Extrapolation from adult efficacy data to the pediatric population describes the reliance on adequate and well-controlled efficacy studies in adults to support a finding of efficacy in the pediatric population. When extrapolation is used, it is generally supplemented by additional studies in the pediatric population, usually pharmacokinetic and safety studies. Extrapolation is based on a prior conclusion that the course of the disease or condition and the effects of the drug are sufficiently similar in adults and pediatric patients to allow extrapolation. A separate study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group (older to younger or vice versa). However, the safety profile can be different in adults when compared to children, and thus safety cannot be extrapolated.

In general, efficacy of sedative medications cannot be extrapolated from adults or older pediatric patients to younger pediatric patients. However, there may be times when Phase 2 studies can serve as proof of concept that the product has the dose-response relationship that is similar to adults, and thus can serve as a basis for utilizing extrapolation. In this case, the Phase 2 study may provide both dose and support for efficacy, leaving safety to be assessed. While safety studies can be difficult and large, the overall study burden is reduced with the introduction of extrapolation.

Pivotal Safety and Efficacy Studies

For approval of a new molecular entity in adult and adolescent patients (age 12 years and older), at least two adequate and well-controlled phase 3 clinical trials are recommended to support either an indication for sedation in the intensive care unit or for procedural sedation.

Pivotal trials in the intensive care population are expected to be conducted in the same population that will use the medication if it is approved and thus should enroll a representative range of patient demographics and disease likely to be encountered in clinical practice. The trials evaluating procedural sedation should enroll patients for a specific procedure, for example, studies of a product for suturing and fracture reduction would probably only include pediatric patients who are ambulatory while studies for lumbar puncture or imaging should include pediatric patients down to the newborn period.

Many efficacy-related outcome measures in children are the same as for adults including time to sedation, time to reemergence and/or discharge, and the success of procedure (performance conditions). Assessing the depth of sedation in children is critical as an unintended level of deep sedation places children at higher risk for respiratory depression and other complications [13]. On the other hand, too little sedation may increase the

incidence of intraoperative awareness or prevent the procedure from being completed successfully [14]. Consensus regarding a "gold standard" for assessing sedation in young children has not been reached [15].

An adequate number of patients to provide sufficient power to demonstrate efficacy is a common challenge in pediatric drug and biologic development. Multiple centers must be utilized to recruit a sufficient number of patients. Some strategies to improve enrollment include multinational trials (especially given that international regulatory authorities such as the European Medicines Agency (EMA) now require development of products for children), going to centers where the procedure requiring sedation is common (a large children's hospital with a busy Emergency Department, a high acuity Neonatal Intensive Care Unit, a large Hematology/Oncology service), and/or utilizing expert networks.

The choice of a control group can be a challenge for these trials. It would be difficult to justify the use of a placebo for sedation, and even more difficult to find parents and guardians willing to enroll their children into a placebo controlled trial. The use of an active comparator is also a challenge as most of the drugs commonly used for sedation, with the exception of midazolam, in pediatrics are not studied or approved by the FDA for this indication. It is difficult to assess the difference in treatment effect between the active control and drug under study if a treatment effect for the active control has not been established. Some companies and Institutional Review Boards have concerns about including an unlabeled product in the study even if that same product is the standard of care.

Safety considerations for study protocols include monitoring of vital signs, in particular, airway, ventilation, oxygenation, and hemodynamic variables. Monitoring must be assessed by personnel who are able to safely rescue patients from oversedation. Laboratory assessments such as a chemistry panel, liver function testing, and complete blood count are needed. Special pediatric subpopulation such as preterm infants need to be assessed for the occurrence of comorbidities of prematurity, such as intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and persistent ductus arteriosus. All patients participating in studies must be monitored in a postanesthetic care setting or equivalent by appropriately trained healthcare providers until discharge criteria have been met.

Patient assessment and management of residual effects of study drugs after criteria for discharge must be incorporated into clinical protocols. For example, protocols must assess when the patient may again safely operate a motor vehicle (adolescents only) or perform cognitively intensive tasks. Some patients may require multiple procedures that require sedation. Pharmacokinetic and other laboratory data may be required to determine the interval when repeat sedation may be performed safely. Study protocols must indicate how adverse events will be appropriately categorized and followed until resolution. Whenever boundary conditions predefined as normal for vital signs are exceeded or when reversal agents or other interventions are needed to prevent an adverse event or sustain clinical vitality, the adverse event should be reported.

Assessing the depth of sedation in pediatric patients is critical. Pediatric patients younger than 6 years of age and those who are developmentally delayed may require deep levels of sedation to control their behavior. In addition, this age group is especially vulnerable to the effects of the sedative medication on respiratory drive, airway patency, and protective reflexes [13]. Since a child's cooperation with a procedure is dependent on the child's chronological and developmental age, it is important to develop and validate assessment metrics that are appropriate for the patient's age and state of development, to include verbal and nonverbal measures. As such, different metrics for smaller pediatric subpoplations may be needed for comprehensive study of the entire age range of pediatric patients likely to be exposed to the drug in medical practice. The appropriateness of sedation scales or scores to be used in young patients or nonverbal patients must be assessed and validated.

Although extrapolation of efficacy may be appropriate, safety cannot be extrapolated from older to younger patients. Since developing systems may respond differently from mature adult organs, some drug interactions and adverse events that occur in pediatric patients may not be identified

in adults or older pediatric patients. However, in general, the nature of the acute safety monitoring of clinical trials is expected to be similar to that required in adults. Evaluation of safety must account for physiologic variations related to maturation and development. Pediatric patients may experience novel adverse events or toxicities of higher severity compared with young mature adults. Extended follow-up may be required to assess developmental progress in patients receiving sedation during period of neuronal expansion and interconnection. Evidence of behavioral abnormalities may result from accelerated neuronal apoptosis that should be sought after administration of medication in suspected drug classes.

With the passage of legislation, and experience of conducting studies in the pediatric population, significant advances have been made in obtaining studies of drugs in children that are adequate and well-controlled. In addition, there have been advances in assessing the safety and both short and long-term use of the sedatives in the developing child. Despite the progress, most products used for pediatric sedation have not been approved for this use by the FDA, and future development should narrow the knowledge gap between what is known about the use of these products in adults and pediatrics.

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Incidence and Stratification of Adverse Events Associated with Sedation: Is There a Benchmark?

20

Mark G. Roback

Background

A significant and growing number of children receive sedation for procedures performed outside of the operating room each year [1–4]. The range of procedures performed and number of different providers of sedation have also been expanded appreciably. While a large number of studies have reported on adverse events occurring in association with procedural sedation in many of these settings [1–14], benchmarks for sedation-related adverse event rates have not been established.

The intent of this chapter is to add some clarity to the concept that the occurrence of adverse events is unavoidable, acceptable rates of adverse events should exist, and sedation providers and programs should be able to compare their individual outcomes to national standards. This chapter will examine current sedation practice outside the operating room and associated adverse events. It will focus on important barriers that must be overcome before meaningful adverse event rates may be determined and best practice guidelines established.

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Introduction

Procedural sedation and analgesia, commonly referred to as "sedation," is the use of anxiolytic, sedative, analgesic, or dissociative drugs to attenuate pain, anxiety, and motion to facilitate the performance of a necessary diagnostic or therapeutic procedure, provide an appropriate degree of amnesia or decreased awareness, and ensure patient safety [15]. The American College of Emergency Physicians defines procedural sedation and analgesia as "a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function" [16]. Comprehensively, we wish to successfully complete necessary procedures for children by providing them sedation, analgesia, and amnesia while maintaining safety.

The depth of sedation experienced by patients is a continuum, dependent on multiple factors including type of drug and dose administered, route of administration, sedation provider in a given setting, and characteristics of the child receiving the sedation [17, 18]. Children can easily move from one level of sedation to a deeper level [19]. Regardless of the depth of sedation that is targeted, a subset of children will become unresponsive and experience loss of airway protective reflexes (general anesthesia) for at least a brief period of time during sedation. The uncertainty of achieving targeted levels of sedation is one of the

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reasons why we believe that children represent the highest risk and lowest error tolerance subgroup of patients who receive sedation outside of the operating room [20, 21]. The result is that children have a higher risk for experiencing sedation-related respiratory depression and life-threatening hypoxia [22]. Importantly, serious adverse events associated with sedation such as cardiopulmonary arrest, apnea, laryngospasm, and pulmonary aspiration, although uncommon, have been reported by many providers, using an array of sedation drugs, in a variety of settings [1–4, 8–11, 23, 24].

Sedation services are provided for children by a range of providers in various settings including sedation units, emergency departments, radiology/imaging suites, hospital wards, and in outpatient settings [1–4, 25, 26]. We should expect that sedation provided by anesthesiologists, pediatric intensivists, emergency and pediatric emergency physicians, certified registered nurse anesthetists, advanced practice nurses, pediatric nurse practitioners, registered nurses, physicians' assistants, pediatricians, and radiologists may have inherent differences [1–4, 27–34]. Sedation providers will differ in the types of patients for whom they provide sedation as well as the variety of procedures for which these patients receive sedation [1, 2]. The drugs administered and routes of administration used will also differ based on depth of sedation targeted. Similarly, the procedures for which sedation is provided may also influence adverse event profiles. Sedation provided by a pediatric emergency physician in the emergency department for a painful procedure will differ from sedation provided by the same individual, in radiology for a Magnetic Resonance Imaging (MRI) scan, which is not painful.

When we propose rates of "acceptable" adverse events, we must consider not only the characteristics of the patient and provider but also the procedure performed and setting as well as sedation drugs used, dose, and routes of administration. As we present the existing current sedation literature in this chapter, we will examine specific characteristics of the sedation event which may be expected to influence adverse event rates. We must also recognize that different providers will define and report adverse events differently based on their training and experience. Regardless of the variables involved in determining acceptable rates of adverse events, the end result of sedation services for children must always be the same: safe, effective sedation provided to facilitate the successful provision of necessary, often times painful, procedures [17, 18].

Setting the Standards for Safety

Determining acceptable rates of adverse events associated with sedation is important due to the potential impact of adverse events on overall patient safety. Most of our knowledge regarding safety of sedation provided to children outside of the operating room comes from small, single-center studies which comment on adverse events but are underpowered to draw definitive conclusions about safety or particular risk factors for adverse events [35]. As a result, current sedation practice guidelines are not evidence-based, but instead are largely derived from incomplete data sets or are the products of consensus opinion [16, 22, 36–44]. Additionally, specific specialty-based practice guidelines exist which may provide divergent recommendations regarding similar sedation practice [22, 36, 39, 44].

Perhaps the most significant improvements in patient safety have been achieved for patients who receive general anesthesia. Anesthesia-related mortality in patients undergoing general anesthesia in operating rooms, has been reduced from 1 in 20,000 in the 1950s to a current rate of approximately 1 in 200,000 [45]. The Closed Claims Project was established in 1984 by the American Society of Anesthesiologists (ASA) to identify anesthetic-related complications and their mechanism of occurrence with the goal of improving patient safety [46]. This dramatic improvement in the safety of general anesthesia was found to be largely due to improvements in how patients were monitored [47]. A recent study of monitored anesthesia care found that appropriate use of monitoring, vigilance, and early resuscitation could have prevented many of the adverse events seen [48]. However, to make further improvement in the safety of anesthesia, to definitively address the

many issues pertaining to anesthesia risk, and to further develop best practice guidelines, prospective multicenter studies designed to examine large numbers of patients must be conducted [49].

Anesthesiologists have developed strategies to improve the safety of general anesthesia by examining critical events. In 2000, Coté and his colleagues published a critical incident analysis of adverse events associated with sedation provided to children outside the operating room. This was a retrospective evaluation of national reporting systems over 27 years [20, 21]. This critical incident analysis attempted to identify factors that contribute to adverse sedation events associated with sedation provided to children undergoing procedures. Factors identified to be associated with adverse outcomes (i.e., permanent neurologic injury and death) included: Sedation which occurred in a nonhospital-based facility, sedation performed with inadequate or inconsistent physiologic monitoring, sedation administered without adequate presedation medical evaluation, sedation performed in the absence of an independent observer with inadequate recovery procedures, and the occurrence of medication errors. Drug overdoses and drug interactions, particularly when three or more drugs were used, were commonly associated with adverse sedation events [21]. Importantly, all routes of administration and all classes of drugs used for sedation were associated with serious adverse events.

The authors of this critical incident analysis of sedation outside the OR concluded that adverse outcomes associated with sedation were most likely related to the *failure of healthcare providers to rescue patients* from sedation-related adverse events, like apnea and oxygen desaturations. They further postulate that individual patient characteristics were less important than failure to rescue patients from the progression of less serious adverse events to serious adverse outcomes.

This important work reinforces the belief that improvements in patient safety related to sedation may be made and acceptable rates of adverse events determined. However, the Closed Claims Project and the critical incident analysis identify characteristics of complications only. No information about the hundreds of thousands of cases which occurred without complication was gathered for comparison. Although the safety of general anesthesia and sedation outside the operating room has improved with strict adherence to monitoring guidelines and timely intervention or rescue from adverse events, most would agree that more work is needed for further progress to be made. Additional data describing the circumstances and conditions surrounding sedation events with and without complications is required to make critical comparisons. From these data, acceptable rates of adverse events may be determined and the goal of developing best practice guidelines to eliminate poor outcomes will be realized.

Disparities in Adverse Event Rate Reporting

A wide range of rates of adverse events (2–26%) associated with emergency department sedation has been reported in recent studies of children [4, 8–11]. The three largest prospective studies of emergency department sedation in children receiving a variety of sedation/analgesia drugs for the breadth of emergency procedures provide a good example of the variability in reported adverse events rates. Despite being conducted in three similar, large urban Children's Hospital emergency departments, these studies report distinctly different rates of common adverse events such as oxygen desaturations (8.6 vs. 13.9 vs. 0.8%) and vomiting (7.2 vs. 1.1 vs. 0.3%) as well as total adverse event rates (17.0 vs. 17.8 vs. 2.3%) [4, 8, 9]. Closer scrutiny of these studies provides some insight into the disparity in adverse event rate reporting. Centers differed with respect to drugs administered, routes of administration employed, use of supplemental oxygen, and the definitions used for oxygen desaturations. Any or all of these factors may be postulated to affect reported adverse event rates. Additionally, the largest of these studies investigated only 2,500 children [4]. Much larger studies are needed to develop adverse event rates of less common

potential complications of sedation such as apnea, laryngospasm, pulmonary aspiration, and cardiopulmonary arrest.

In another example, comparisons between single center studies showed significant disparities in adverse event reporting despite having similar settings (emergency departments), types of procedure performed (painful), and sedation drug (ketamine) administered. Only the route of administration differed (intravenous vs. intramuscular) in these studies – yet reported adverse event rates such as vomiting still varied considerably from 3.8 to 18.7% [4, 8, 10, 50–55].

Adverse event rates reported with sedation provided with propofol is a further example of disparities in adverse event reporting despite use of a common agent. With the administration of propofol, the variability of reported adverse event rates such as oxygen desaturation (0–30%) and apnea necessitating the use of positive pressure ventilation (0–2.5%) may be due to differences in providers (pediatric intensivists vs. emergency physicians), setting (sedation unit vs. emergency department vs. radiology), type of procedure (painful vs. not painful), and presence of coadministered analgesic such as fentanyl [3, 56–64]. In emergency department studies of sedation with propofol-based regimens, rates of adverse events varied from low 3.5% [65] to high of 31% [55] and 33% [57]. One study of sedation using propofol with fentanyl reported complications in an extremely high rate (84%) of patients [66]. Given the high degree of variability of adverse event rates observed when current studies are compared, it is impossible to draw conclusions about the effectiveness of sedation and safety.

Clinically apparent pulmonary aspiration is an important, although infrequently reported, complication of sedation outside the operating room [1–3, 24, 25, 67]. As part of the assessment of patients about to receive sedation or anesthesia, careful history addressing recent oral intake is undertaken with the goal of minimizing the risk of pulmonary aspiration by adhering to preprocedural fasting recommendations [68]. Clinically apparent pulmonary aspiration events have been reported to have occurred in association with sedation in settings where ASA preprocedural fasting guidelines are routinely followed such as dedicated sedation units [1–3] and for radiological procedures and bronchoscopy [25, 26]. However, in emergency departments, where adherence to preprocedural fasting guidelines has not been shown to be rigorously applied [5–7], aspiration has never been reported to have occurred in a child [43, 69, 70].

Examples of the range of rates of adverse events are presented in this section to emphasize that multiple factors contribute to the incidence of adverse events in any given setting. In order to begin to understand these interactions, we must ensure that comparisons are made that control for as many of these factors as possible. Reasons for differences in adverse event reporting may be obvious such as the rate of respiratory depression associated with propofol as opposed to that observed with oral chloral hydrate. Further reasons for disparities in adverse event reporting may be as basic as how we define and report adverse events of interest.

Definition of Adverse Events and Reporting Recommendations

In addition to the clinical parameters described in the previous section, some of the variability of reported rates of adverse events associated with sedation provided outside the operating room may be attributed to existing widespread differences in definitions of adverse events and reporting practices. The rate of total adverse events is dependent on how these events are defined and which events individual providers and sedation services choose to report as significant. For example, an anesthesiologist may consider sonorous breathing resulting in a pulse oximeter reading of 87% (relieved by a simple jaw thrust) as inherent to propofol sedation and not report its occurrence as an adverse event. By contrast, a pediatric emergency physician may respond exactly the same way to an identical event with similar results yet report it as partial airway

obstruction and oxygen desaturation. In another example, if oxygen desaturation is defined as an oximeter reading <90% in room air for greater than 30 s, a child who desaturates from 100% at the beginning of sedation to 90% during the procedure and who responds positively to an airway maneuver and the administration of oxygen, would not be reported as having experienced an adverse event.

Efforts to develop evidence-based practice guidelines designed to prevent the occurrence of adverse events have been limited by an inability to aggregate adverse events resulting from existing studies. As described above, sedation practice varies widely and the rate of adverse events is reported inconsistently. An important reason for this variability is that investigators do not have a standardized set of definitions and reporting guidelines to follow [4, 5, 8, 9, 59, 62, 71]. In order to facilitate comparisons between studies and the aggregation of data from multiple studies, definitions to describe sedation practices, interventions, and adverse events must be developed and routinely used. Only after clear definitions for adverse events and recommendations for reporting exist and are consistently followed in studies of large numbers of sedation, will meaningful adverse events rates be established. Once standard adverse event rates are established, sedation providers and programs may accurately and critically assess their work.

To address the wide disparities that exist in the reporting of adverse events, the Quebec Guidelines for sedation provided to children in the emergency setting were devised by consensus of an expert panel of pediatric emergency physicians and pediatric anesthesiologists [15]. Intervention-based definitions for adverse events were chosen because the panel believed that this framework would yield the greatest possibility of uniform data collection for clinically important events. Definitions using this approach require specific clinical criteria to be present (e.g., decrease in oxygen saturation) *and* for one or more interventions (e.g., tactile stimulation and administration of blow-by oxygen) to be performed with the intention of treating or managing the event [15]. Table 20.1 provides a list of

Table 20.1 Intervention-based definitions for sedation-associated adverse events

Averse events	Interventions performed in response
Oxygen desaturation	Vigorous tactile stimulation
	Airway repositioning
	Suctioning
	Oral or nasal airway placement
Apnea: central vs. obstructive (partial vs. complete)	Administration of reversal agents
	Supplementing/increasing oxygen
	Application of positive pressure ± ventilation with bag mask
	Tracheal intubation
Clinically apparent pulmonary aspiration	Extended observation or admission to hospital
Retching/vomiting	Administration of antiemetic
Cardiovascular events	Chest compressions
Bradycardia	Administration of medications
Hypotension	IV fluid administration
Excitatory movements	Procedure was delayed, interrupted, or not completed
Paradoxical response to sedation	Administration of reversal agents
	Administration of sedation drugs
Unpleasant recovery reactions	Allocation of additional personnel to care for the patient
	Delay in discharge or disposition
Permanent complications (neurologic injury or death)	

adverse events that should be documented and reported as recommended by the Quebec Guidelines, as well as examples of interventions that may be performed in response to these events. Appendix provides complete Quebec Guidelines recommendations for definitions of adverse events within a template which may be used for data collection and documentation.

The Quebec Guidelines were intended to provide researchers with a template on which adverse events may be consistently documented and reported with the purpose of consistently collecting data which will allow uniform data sets and meaningful comparisons of sedation studies. Although the guidelines were developed for use in children receiving sedation in the emergency department, an accompanying editorial states that the Quebec Guidelines are broadly applicable to all forms of sedation research or adverse event monitoring [72]. More directly, despite the pediatric intent, each definition and recommendation applies readily to adults. This approach and the principles put forth extrapolate to any setting in which sedation is performed [17, 18, 72].

Once data is generated from multicenter studies of large populations of patients using standardized definitions and reporting schemes, meaningful adverse event rates may be established and definitive clinical care guidelines may be devised that will improve our ability to ensure the safety of sedation provided to children outside of the operating room.

Multicenter Investigations

Until just recently no studies of sufficiently large numbers of children who received sedation outside the operating room existed to allow for evaluation of acceptable rates of adverse events. The Pediatric Sedation Research Consortium (PSRC) has published an observational study of over 30,000 children who received sedation at 26 institutions for mostly elective procedures (8% emergency), performed by different providers (pediatric intensivists 28.4%, emergency physicians 27.9%, and anesthesiologists 19.2%) using mostly the following drugs singly or in combination: propofol (50.1%), midazolam (27.1%), ketamine (13.6%), or chloral hydrate (11.7%) [1]. In this large cohort of children, they observed zero deaths, 1 cardiac arrest, 1 case of pulmonary aspiration, 13 episodes of laryngospasm, and 73 patients experienced unexpected apnea. All patients were successfully rescued from potentially poor outcomes and 1 in 1,500 sedation events resulted in unexpected admission to the hospital.

A subsequent study examined propofol administration by a variety of specialists, under circumstances similar to their first study in almost 50,000 children [2]. Again, no deaths were observed; however, apnea or airway obstruction was common (5.75%) and cardiac arrest ($n=2$), pulmonary aspiration ($n=4$), and laryngospasm ($n=96$) occurred. The authors emphasized that safety depends on providers' ability to identify potentially serious adverse events, usually respiratory in nature, and provide appropriate rescue. Further data is needed to identify specific patients who may be at an increased risk for adverse events and to establish rates of adverse events in the emergency setting and in those receiving sedation drugs other than propofol.

Ketamine has become the most commonly administered drug for the sedation of children in the emergency department [17, 18, 38, 39, 41, 73–75]. A recent individual patient data meta-analysis of over 8,000 ketamine administrations to children in 32 emergency departments sheds some light on adverse events rates and risk factors for emergency sedation with ketamine. Green et al. report an overall incidence of airway and respiratory adverse events of 3.9% [73]. Age younger than 2 years and age 13 years or older, high intravenous dosing and coadministration of anticholinergic or benzodiazepine were independent predictors of airway or respiratory adverse events. Although this study represents the largest sample of children receiving emergency department ketamine sedation to date and provides important information, the study design did not allow for definitions of adverse events to be

determined *a priori*, and many important clinical variables were not included.

Prospective studies of large cohorts of children, using standardized definitions and reporting structures for adverse events, are required to generate the data needed to carefully examine the multitude of factors that contribute to adverse events before meaningful "acceptable" adverse event rates may be established.

Future Directions

As described previously, the works of the Pediatric Sedation Research Consortium and the ketamine individual patient data meta-analysis are important first steps toward generating the data required to carefully assess sedation practice in children outside the OR [1, 2, 73]. Recently, the World Society of Intravenous Anesthesia (World SIVA) established an International Sedation Task Force (ISTF) represented by 26 members from multispecialties, both adult and pediatric, from 11 countries. The ISTF has presented an Adverse Event Reporting Tool designed to standardize the collection of sedation outcome data (adult and children) worldwide (Table 20.2) [76]. This tool is an open-access web-based tool, available to providers globally (www.AESedationReporting.com or www.InternationalSedationTaskForce.com). The data collected will be available to individual and institutional users and will, in addition, populate the global ISTF sedation database. The collection of large data from multi specialists globally will be an important first step to identify and carefully evaluate the range of variables which effect sedation-related adverse event rates. Such studies must be broad reaching in scope yet flexible enough to consider new developments in sedation techniques and monitoring as well as the use of the ever-emerging new sedation drugs that become available.

Only through rigorous adherence to the use of standardized adverse events definitions and reporting structures (such as described in the Quebec Guidelines and by the ISTF), will standardized data sets be compiled. This will allow for the aggregation of data and meaningful comparisons of sedation studies. National and international multispecialty collaboration will be required to develop databases with sufficient patient numbers and the clinical data required to develop and evaluate sedation practice based on patient populations and providers, procedures performed, and drugs administered. The feasibility of such a collaborative endeavor requires not only cooperation of multiple specialties using cutting-edge data collection technology but also a level of funding which to date has not been realized.

Summary

From the discussion presented here, we can conclude that adverse event rates will vary depending on individual patient characteristics, procedures performed, sedation drugs and doses employed, providers of sedation, and the setting in which patients receive care. In addition, the definitions used to identify adverse events and existing reporting structures will also impact on rates of adverse events observed. As studies of larger numbers of children are performed using standardized definitions and reporting of adverse events, we will gain a clearer picture of what may be the expected and acceptable adverse event rates. Further multicenter, prospective research of international populations of children who receive sedation will identify risk factors for adverse events so that true evidence-based sedation best practice guidelines may be established.

Standards of adverse events rates will vary based on the characteristics of the sedation experience as described above. However, patient safety will ultimately be ensured by the careful assessment of risks and benefits of sedation which is performed in carefully monitored and controlled clinical settings by skilled providers prepared to provide cardio-respiratory rescue when needed.

Table 20.2 International Sedation Task Force Adverse Event Sedation Reporting Tool (www.AESedationReporting.com)

World SIVA adverse sedation event recording tool configured for a web page or paper form

Step 1: Was there one or more adverse events associated with this sedation encounter?

o No, this form is now complete.
o Yes, fill out remainder of form below.

Step 2: Please DESCRIBE the adverse event(s). Check all that apply.

Minimal risk descriptors	*Minor risk descriptors*	*Sentinel Risk descriptors*	
o Vomiting/Retching	o Oxygen desaturation (75–90%) for <60 seconds	o Oxygen desaturation, severe (<75% at any time) or prolonged (<90% for >60 seconds)	o Other specify below
o Sub clinical respiratory depression[a]	o Apnea, not prolonged	o Apnea, prolonged (>60 seconds)	
o Muscle rigidity, myoclonus	o Airway obstruction	o Cardiovascular collapse/shock[g]	
o Hypersalivation	o Failed sedation[e]	o Cardiac arrest/absent pulse	
o Paradoxical response[b]	o Allergic reaction without anapaylaxis		
o Recovery agitation[c]	o Bradycardia[f]		
o Prolonged recovery[d]	o Tachycardia[f]		
	o Hypotension[f]		
	o Hypertension[f]		
	o Seizure		

Step 3: Please note the INTERVENTIONS performed to treat the adverse events(s) Check all that apply.

Minimal risk	*Minor risk*	*Moderate risk*	*Sentinel intervention*	
o No intervention performed	o Airway repositioning	o Bag valve mask assisted ventilation	o Chest compressions	o Other, specify below
Administration of:	o Tectile stimulation or the administration of:	o Laryngeal mask airway	o Tracheal intubation or the administration of:	
o Additional sedative (s)	o Supplemental oxygen, new or increased	o Oral/nasal airway	o Neuromuscular blockade	
o Anti-emetic	o Antisialogogue	o CPAP or the administration of:	o Pressor/epinephrine	
o Antihi stamine		o Reversal agents	o Atropine to treat bradycardia	
		o Rapid IV fluids		
		o Anti convulsant IV		

Step 4: Please note the OUTCOME of the adverse event(s). Check all that apply.

Minimal risk outcome	*Moderate risk outcome*	*Sentinel outcome*	
o No adverse outcome	o Unplanned hospitalization or escalation of care[h]	o Death	o Other specify below
		o Permanent neurological deficit	
		o Pulmonary aspiration syndrome[i]	

Step 5: Assign a SEVERITY rating to the adverse event(s) associated with this sedation encounter.
o It there are any options checked in the Sentinel columns above, then this is a **Sentinel**[j] adverse event.
o If the most serious option(s) checked above are Moderate risk, then this is a **Moderate**[k] risk adverse event.
o If the most serious option(s) checked above are Minor risk, then this is a **Minor**[l] risk adverse event.
o If the most serious option(s) checked above are Minimal risk, then this is a **Minimal**[m] risk adverse event.

Additional details (including "other" entries):

[a]"Subclinical respiratory depression" is defined as capnographic abnormalities suggesting respiratory depression that do not manifest clinically

[b]"Paradoxical response" is defined as unanticipated restlessness or agitation in response to sedatives

[c]"Recovery agitation" is defined as abnormal patient affect or behaviors during the recovery phase that can include crying, agitation, delirium, dysphoria, hallucinations, or nightmares

[d]"Prolonged recovery" is defined as failure to return to baseline clinical status within 2 h

[e]"Failed sedation" is defined as inability to attain suitable conditions to humanely perform the procedure

[f]Alteration in vital signs (bradycardia, tachycardia, hypotension, hypertension) is defined as a change of >25% from baseline

[g]"Cardiovascular collapse/shock" is defined as clinical evidence of inadequate perfusion

[h]Examples of "Escalation of care" include transfer from ward to intensive care, and prolonged hospitalization

[i]"Pulmonary aspiration syndrome" is defined as known or suspected inhalation of foreign material such as gastric contents into the respiratory tract associated with new or worsening respiratory signs

[j]"Sentinel" adverse events are those critical enough to represent real or serious imminent risk of serious and major patient injury. Once recognized, they warrant immediate and aggressive rescue interventions. Once clinically concluded, they warrant immediate reporting within sedation care systems, and the highest level of peer scrutiny for continuous quality improvement

[k]"Moderate" adverse events are those that, while not sentinel, are serious enough to quickly endanger the patient if not promptly managed. Once clinically concluded, they warrant timely reporting within sedation care systems, and periodic peer scrutiny for continuous quality improvement

[l]"Minor" adverse events are those encountered periodically in most sedation settings, and those pose little threat given appropriate seditionist skills and monitoring

[m]"Minimal" adverse events are those that alone present no danger of permanent harm to the patient

Appendix

Appendix E1. Recommended documentation for sedation research.

A. SEDATION DOCUMENTATION

1. Pre-Sedation Behavioral State

Definition: The patient's behavioral state immediately prior to sedation.

1. Indicate the state that best describes the child's behavior immediately prior to the administration of the sedation drugs:
   - ☐ Calm (eg, not crying)
   - ☐ Agitated but responds to comforting (eg, briefly stops crying)
   - ☐ Agitated and does not respond to comforting (eg, continuous crying)

2. Efficacy of Sedation

Definition: A successful sedation creates conditions necessary to safely facilitate completion of a procedure through attenuation of pain, anxiety and movement with amnesia or decreased awareness. Patient must fulfill all criteria for a sedation to be considered successful.

1. Sedation was efficacious ☐ YES ☐ NO
   If YES, indicate which of the following criteria were met during the sedation
   - ☐ The patient does not have unpleasant recall of the procedure
   - ☐ The patient did not experience a sedation-related adverse event, resulting in the abandonment of the procedure
   - ☐ The patient did not experience a permanent complication
   - ☐ The patient did not have an unplanned admission to hospital or prolonged ED observation
   - ☐ The patient did not actively resist or require physical restraint for completion of the procedure

B. ADVERSE OUTCOME DOCUMENTATION

1. Oxygenation

1.1 Oxygen Desaturation ☐ YES ☐ NO

Definition: Oxygen desaturation AND one or more intervention(s) are performed with the intention of improving the saturation

1. Baseline oxygen saturation on room air prior to PSA _____%
2. Oxygen delivered at start of Sedation phase ☐ NO ☐ YES
   If YES, Method of oxygen delivery: ☐ nasal canula ☐ blow-by ☐ face mask ☐ face mask + non-rebreather
   Flow rate delivered: _____litres/minute
3. Indicate the interventions performed in response to the oxygen desaturation *(indicate ALL that apply)*
   - ☐ Vigorous tactile stimulation
   - ☐ Airway repositioning
   - ☐ Suctioning
   - ☐ Supplementing/increasing oxygen
   - ☐ Oral or nasal airway placement
   - ☐ Application of positive pressure +/- ventilation with bag mask
   - ☐ Tracheal Intubation
   - ☐ Other _____
4. Lowest reliable oxygen saturation measured during the sedation _____%

2. Ventilation

2.1 Apnea: central ☐ YES ☐ NO

Definition: Cessation or pause of ventilatory effort AND one or more intervention(s) are performed with the intention of stimulating or assisting ventilation.

1. Indicate the criteria used for recognition *(indicate ALL that apply)*
   - ☐ Visual confirmation of cessation/pause of ventilation
   - ☐ Cyanosis
   - ☐ Oxygen desaturation
   - ☐ Loss of CO_2 waveform
   - ☐ Other _____
2. Indicate the interventions performed in response to the apnea (*indicate ALL that apply)*
   - ☐ Vigorous tactile stimulation
   - ☐ Administration of reversal agents
   - ☐ Other _____
   - ☐ Application of bag mask *with* assisted ventilation
   - ☐ Tracheal intubation

2.2 Apnea: Obstructive

2.2.1 Partial Upper Airway Obstruction ☐ YES ☐ NO

Definition: Manifested by stridor, snoring OR chest wall and suprasternal retractions AND one or more intervention(s) are performed with the intention of relieving the partial airway obstruction.

1. Indicate the criteria used for recognition *(indicate ALL that apply)*
   - ☐ Stridor
   - ☐ Snoring
   - ☐ Chest wall or suprasternal retractions
   - ☐ Oxygen desaturation
   - ☐ Other _____

Source: From Bhatt et al. [15]. Reprinted with permission from the American College of Emergency Physicians.

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Medicolegal Risks and Outcomes of Sedation

21

Steven M. Selbst

Introduction

Most children who receive sedation outside the Operating Room have a good outcome and benefit from efforts to reduce pain and anxiety during a procedure [1, 2]. However, administration of sedative and analgesic agents to children in the outpatient setting always carries some risk to the patient. One study showed that up to 17% of pediatric procedural sedations have some type of complication [3]. Most adverse events are respiratory and 1/200 requires interventions to maintain a patent airway and to ventilate the patient. One in every 1,500 sedations results in an event that requires unanticipated admission to the hospital [3]. Whenever a child has a bad outcome after receiving sedation, there is potential liability for the provider and it is quite possible that a malpractice suit will follow. There have been several settled cases that involve problems with sedation of children. These malpractice cases do not necessarily reflect poor care by the health professional, but that care will certainly be scrutinized whenever there is a lawsuit. It is wise to take precautions to prevent adverse outcomes and subsequent litigation.

When litigation ensues, the hospital or center where the event took place, the physician who ordered the sedative agent, and the provider who gave the medication may all be named in the lawsuit. Most malpractice lawsuits result in an out-of-court settlement, or they are dropped altogether. Only about 10% reach a jury verdict [4]. Still, these legal actions can be quite burdensome and emotionally draining. They are also quite expensive.

Patients and families are likely to sue a hospital or a physician whenever there is a bad outcome, if they perceive there was negligent care and when there is poor communication with the physician. Some families sue to seek revenge against a physician with whom they are angry or unhappy. Others sue to obtain resources they will need to care for a handicapped child. Others sue to relieve their own guilt, and some to "save another patient from the physician" who injured their child [5]. Often the suits are instigated by a relative (perhaps a physician or a nurse) who implies that the treatment given to the child fell below the standard of care. The Standard of Care is defined as that which a reasonable physician in a particular specialty would have given to a similar patient, under similar circumstances. Because most clinicians have similar access to information and knowledge, most often they are held to a national standard of care, no matter where the individual practices [6].

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Preventing Litigation

Malpractice lawsuits are an unpleasant and undeniable part of medical practice. However, they are not necessarily inevitable. Many malpractice lawsuits involving sedation are predictable and preventable just like many pediatric diseases and childhood injuries. Some malpractice lawsuits can be prevented if the medical staff is committed to practicing "good medicine," communicating well with family members and other hospital staff, and documenting the good care that is delivered [6].

Practice "Good Medicine"

The most effective way to prevent a malpractice lawsuit is to prevent the adverse outcome from occurring (see Table 21.1). Clinicians who are responsible for sedating a child should be qualified and credentialed. Hospitals and other medical centers must develop criteria and training to credential individuals caring for sedated children. There is no universal rule on what the credentialing process must entail. Many centers require the clinician to be certified in PALS, BLS, and perhaps take a course or complete an online module about specific sedative agents. Some recommend simulation-based training of nonanesthesiologists to improve patient safety during pediatric sedation [7]. While training may vary at different institutions, the clinician must be thoroughly knowledgeable about the agents they use and their potential complications. The clinician must anticipate a deeper level of sedation than planned. Furthermore, the clinician must have appropriate skills to rescue a sedated patient if there is a complication.

Table 21.1 Preventing adverse outcomes

Provider must be qualified and credentialed
Provider must have skills to rescue patient
Provider must have knowledge of medications and potential complications
Provider must prepare for a deeper level of sedation than anticipated
Perform a presedation evaluation
Consult anesthesia for high-risk cases
Check medications and dosages prior to administration
Observe patients until back to baseline
Develop and follow hospital policies and procedures

Clinicians who work in a free standing facility (such as a dental office, gastroenterology suite) must be particularly cautious and they must have a plan in advance to activate emergency medical services (EMS) for help when there is an adverse event. They must have proper equipment available and the necessary skills to use this equipment appropriately while awaiting help [8]. In the event of a bad outcome, practitioners using sedative agents in an office setting, offsite from the hospital, will likely be held to the same standards as other clinicians who use the same agents.

It is wise to avoid the practice of giving sedating medications at home, prior to a procedure, as this is associated with an increased risk for airway obstruction while parents drive to the hospital [9]. Furthermore, the clinician should have a clear understanding of the goals of sedation and then use the drugs wisely to achieve the intended depth of sedation [10].

Pre Sedation Evaluation/Decisions

The clinician providing sedation must carefully evaluate the child prior to administration of any sedative agent. Inadequate evaluation prior to the sedation has been found to be a factor in many adverse events [9]. A presedation health evaluation should at least include the patient's age, weight, allergies, medications, relevant family history, and past medical history including physical abnormalities, history of snoring, and neurologic impairment that may increase potential for airway obstruction. A focused assessment of the airway is crucial; assess for large tonsils or anatomic airway abnormalities that may increase the risk for airway obstruction. The exam should always include vital signs [8, 10].

It is wise to involve the Anesthesia Department for high-risk patients – those with snoring, stridor, sleep apnea, craniofacial abnormalities, abnormal airway, vomiting, gastroesophageal reflux, bowel

obstruction, asthma exacerbation, pneumonia, and complex medical problems such as cardiac disease, hypovolemia, or neuro-muscular disorder. Also, involve the Anesthesia Department for children younger than 1 year of age or those with an ASA classification greater than 3 [8, 11].

Double check medication dosages before any drugs are given. Take time to make sure that all necessary equipment and medications are in place before giving sedative agents. The SOAPME checklist is familiar to many and reminds the clinician to plan in advance (Suction, Oxygen, Airway (appropriate-sized equipment), Pharmacy (drugs needed), Monitors, Equipment (perhaps a defibrillator)) [8, 11]. The Joint Commission advocates a "time out" before any medication is given to verify the correct patient, site, and medications [12]. Anticipate complications such as laryngospasm. Have a back-up plan for complications before they arise. The Joint Commission emphasizes the concept of "sedation rescue," which is essential to safe sedation [12]. The ability to rescue a patient after an adverse event is also emphasized by AAP guidelines [8]. Plan ahead and decide who will be consulted and how an emergency will be managed.

Medication Errors

Whenever sedative or analgesic medications are used, there is always a chance for error. Often these errors are preventable. One study found that there are 3.99 errors for every 1,000 medications ordered for hospital patients and many are potentially serious [13]. This is due in part to look-alike and sound-alike drugs. Hospitals and clinicians must be careful with these and keep the medications separated and clearly labeled.

Many other medication errors are due to incorrect computation. Some of these may be preventable by computer technology where only approved drug doses are accepted by the computer. Serious medication errors often involve a misplaced decimal point, which can result in a tenfold error. It is thus recommended when writing medication orders, to place a zero before a decimal point to express a number less than one (e.g., 0.5 mL). However, one should never use a terminal zero (e.g., 5.0), since failure to see the decimal point may result in the patient getting 10 times the dose desired. Likewise, avoid abbreviations such as: "cc, u" as poor handwriting can result in misinterpretation of these symbols. Preventable errors may also occur when the healthcare provider fails to obtain an adequate history of allergies, or fails to read the record that documents an allergy [14].

Postsedation/Discharge

Observe the patient for an appropriate period of time after giving sedation. No child who receives sedation should be discharged until he/she meets criteria proposed by the AAP [8]. Before discharge, the child should have normal cardiovascular function, an intact gag reflex, and a patent airway. The state of hydration should also be adequate. The child should be easily aroused and able to sit and talk, if age appropriate. Younger children or those with neurologic dysfunction should be close to their presedation level of function before discharge. Consider prolonged observation if the only adult present has to drive the car or if a child has an underlying medical problem, such as neurologic impairment, partial airway obstruction, minor complications during the sedation, or previous problems with sedation [8]. Provide a 24 h phone number that parents can call with any questions about their child's sedation or behavior [11]. Give instructions about limitation of activity and appropriate dietary precautions. Premature discharge of a sedated patient from the ED can have disastrous consequences.

Policies and Protocols

Hospitals must develop and publish policies and procedures regarding sedation. Practitioners involved with sedation of a pediatric patient must be aware of them and follow the policies and protocols. Often, attorneys will use such hospital standards to show that a clinician deviated from the protocol [15]. Thus, it is important to make

sure that hospital protocols are reasonable, so that clinicians are comfortable with them and they do not lead to unreasonable monitoring or other requirements. For instance, capnography is "encouraged" for sedated children in AAP guidelines [8]. However, if the hospital does not routinely require end-tidal CO_2 monitoring for every sedated patients, this should not be found as a requirement in the Policy and Procedure manual of the hospital.

Furthermore, proper supervision of trainees is important. Trainees often order sedation for children. Lack of supervision is a common factor in medical errors by trainees and resulting malpractice lawsuits [16].

A few years ago, the Joint Commission found significant variation in the level of care provided to children depending on where the sedation was administered in the same institution (emergency department, clinic, radiology suite, etc.) [12]. They mandated that each institution develop its own specific protocols for patients receiving sedation that carries the risk of loss of protective reflexes. The Joint Commission also specified that *the standard of care be the same for all sedated patients throughout the hospital*. The institution must standardize its documentation process in terms of history, physical exam, and events of the procedure and recovery phase. Guidelines for informed consent for procedures must be unvaried throughout the institution. Furthermore, monitoring guidelines and skills of the personnel who are providing care for the sedated child must be uniform in the institution [12]. Standards for how long a child must be "NPO" (nothing by mouth) before receiving sedation must also be standardized throughout the hospital. Though NPO guidelines have been challenged recently due to lack of evidence, hospitals must still have a consistent policy. The NPO policy should not be different in the ED than elsewhere in the hospital. Even in the ED, use of sedation must be preceded by an evaluation of food and fluid intake. However, this policy may take an emergency situation into account and the fasting interval is sometimes shortened in the Emergency Department (ED). The hospital policy should reflect the fact that in an emergency, when proper fasting cannot be ensured, the increased risk of sedation must be weighed against its benefits. In general, use the lightest effective sedation in these emergency situations [8].

Hospital policy should also define which clinicians can order or administer specific sedative medications. Many hospitals permit nonanesthesiologists to administer agents such as propofol or ketamine after specific training, whereas some prohibit this. Such decisions are generally left to the discretion of the individual hospital, as the Standard of Care allows nonanesthesiologists to use such medications within appropriate guidelines. Package insert information about sedative agents is important, but does not necessarily dictate clinical practice. In the event of a malpractice lawsuit involving sedative agents, evidence-based research and clinical usage protocols will be considered as well. If such evidence demonstrates safe and effective outcomes for agents utilized in procedural sedation in the ED, the clinician should be able to defend the administration of agents such as propofol, when used properly.

Hospitals should specify which medications can or cannot be administered by nursing staff. Such policies must be guided by local laws and regulations. In many states, nurses are not permitted to give certain sedative agents in the ED. It is wise for nurses and other practitioners to follow these states, local, and hospital regulations. In the event of a bad outcome with sedation, such regulations would undoubtedly be called up and deviation from these rules may be difficult to defend.

Finally, hospital policies should address the issue of photographs and video recording of patients who receive sedation. In general, images that capture the appearance of a patient as part of his or her medical care become part of the patient's medical record. Thus, they are subject to legal scrutiny as any other part of the record and they can be used as evidence in the event of a malpractice lawsuit. However, it is not clear if images acquired by a treating physician for purposes other than medical care (such as for use in publications, lectures, or a clinical trial) would be considered part of the medical record. A court's classification of these images may be influenced by the expectation of the patient and his/her

guardians. It is unlikely that a court would view images captured by someone who is not the child's physician as part of the record [17].

Clinical Guidelines

Several organizations have published guidelines to assist healthcare professionals in sedating children in a safe manner. The American Academy of Pediatrics recently revised and published guidelines for sedation in 2006 [8], as did the American College of Emergency Physicians in 2008 and 2011 [18, 19]. Those involved with pediatric sedation should be familiar with published clinical care guidelines and if these are not followed, he/she should be able to defend the deviation. In many cases, a particular patient does not fit the guidelines, and if the clinician acts reasonably, he/she is not bound to these. However, guidelines from major organizations like the AAP will have great impact in court. A guideline does not automatically become the standard of care. A guideline must be widely accepted by a specialty before it is used as the standard of care in a malpractice case [20].

Guidelines for fasting prior to sedation are consensus based rather than evidence based and thus they are debatable. However, one should not disregard the fasting status of the patient entirely [8, 10, 18, 21, 22]. Documentation of the last oral intake is good practice and a Joint Commission requirement [12]. It is prudent to assume that all patients in the ED have a full stomach when planning the use of sedatives or analgesics. Consider the risk benefit ratio based on when the child last ate and the urgency of the procedure. Such consideration will help prevent an adverse event and will help defend any litigation.

Communicate Well

It is very important for those involved with sedation to communicate well with families. The clinicians should listen well and speak clearly. Tell the parents/family what to expect. Keep the family informed as the procedure and sedation evolve. Develop a sense of trust with the family. One effective way to do this is to show compassion [23]. The clinician's dress, posture, and manners also impact on the ability to develop a sense of trust.

Failure to communicate is often a factor in malpractice lawsuits. One study [24] showed that 70% of lawsuits involve communication style or the clinician's attitude. Patients who sued reported that the physicians involved inadequately explained the diagnosis or treatment to the family. They failed to understand the patient/family perspective, and often discounted or devalued the patient/family views. In many cases the family felt rushed. In Hickson's study of parents who sued, it was also found that families were dissatisfied with patient/doctor communication [5]. In this study, 13% reported the doctor would not listen, 32% reported the doctor did not talk openly, 48% indicated the doctor attempted to mislead them, and 70% said the doctor did not warn them about their baby's outcome.

Informed Consent

Informed consent is more than just obtaining a parent's signature on a piece of paper. The family of a child who receives sedation is entitled to information about the procedure and the medications to be used. Parents have the right to know about the risks and benefits of the treatment to be given to their child, and any alternatives available. Their consent should be obtained prior to administration of any sedative agents. A general consent form signed at the time of arrival to the outpatient facility does not usually imply consent for use of sedation and analgesic medications. Separate consent for sedation is advised. Whether consent should be in written or verbal form depends on local, state, and institutional requirements. In many states, verbal consent is adequate for most emergency procedures. Written consent forms have value in educating the guardian with respect to the procedure, and they may provide some protection to the caregiver by documenting the steps taken to inform the family. However, signing a form does not

necessarily imply informed consent [25, 26]. The guardian may still claim the risks and benefits were not adequately explained. If a specific consent form is not used, it must be clearly documented in the record as to what the parents were told and that they gave verbal agreement. In a true emergency, informed consent is not needed; it is implied and assumed that a reasonable parent would want immediate necessary care.

Pennsylvania law defines informed consent as giving the consenting person a description of the procedure and the risks and alternatives such that a "reasonably prudent person" would be able to make an informed decision about whether to undergo the procedure. This patient focused concept of informed consent is followed by most states. The parents could conceivably bring a lawsuit against a physician for failing to obtain informed consent if they are not told of a risk of the treatment and the child suffers harm from the sedation. The parents would have to prove that reasonable people, properly advised, would not have consented to the procedure had they been previously informed [26].

Parents should be informed consumers. Information given to the guardian should include objectives of the sedation, anticipated changes in behavior during and after the sedation. Parents should be informed of alternatives such as use of local anesthesia, regional anesthesia, general anesthesia in the Operating Room, and alternate routes of administration. One study identified that parents most often wanted information regarding induction, adverse events, emergence reactions, and pain relief [27].

Information should be given in a clear straightforward manner. The care provider should be sure the guardian understands the information given, and it may be useful to ask the parent to paraphrase what they have been told. If a serious complication could result from treatment, then the caregiver should inform the family of all but the most remote risks. On the contrary, if the potential injury is minor, the family need only be informed of the risks that are common [8, 10, 28, 29]. No parent should be forced to make a specific decision for a child. Most parents desire the opinion of the experienced caregiver, and advice from the doctor helps them make a reasonable determination of what is best for their child. Table 21.2 summarizes important features of the informed consent process.

Table 21.2 Important items of informed consent

Provide a clear explanation
Describe risks and benefits of sedation
Review medication effects, anticipated change in behavior, possible emergence reactions, pain relief
List all potential serious complications
List potential common, minor complications
Discuss alternative treatments – local or general anesthesia
Make sure the family understands the information

Communicate Well with Staff

Good communication between staff members involved with sedation is also essential. Do not demean other staff members in front of parents. Instead, it is best to "manage up" and praise other staff in front of families. Avoid joking or stray comments nearby families as they may misinterpret what is said or get a wrong impression that the staff is not concentrating on their child. Transfer information carefully. There are numerous errors related to poor sign-out of information among staff. Change-of-shift can be dangerous, as information can be lost during hand-offs [30].

Document Carefully

Careful documentation of the use of sedatives and analgesics is extremely important. The child's medical record may be the first item reviewed by an attorney and a consulting expert physician in determining whether a complication was the result of negligence. Thus the medical record could be your best defense or the plaintiff's best witness. A complete and thorough record may prevent a lawsuit, or at least it will help the healthcare provider to defend a legal action. Often, there is an extended length of time between the patient encounter and a subsequent malpractice suit. A complete, well-prepared record will then prove very helpful when recall of the event

has faded. The chart should reflect a neat, professional appearance and it should be maintained as if it were a public document [6, 25].

If an inpatient or outpatient chart already exists, there is no need to repeat the information previously documented. However, a brief note to indicate that the chart was reviewed before administration of sedative agents is recommended. Indicate the child's presedation status. Note that the patient's condition has not changed since arrival or since the last exam in the record [8].

A well-designed, time-based record will make it easier to find and record essential information. The patient's weight and allergies should be placed in an obvious location in the record so they can be easily noticed when medications are ordered. Checklists in the record may serve to remind the caregiver to ask specific questions or perform a specific part of the physical examination [11].

Documented history should include the child's age and abnormalities of the airway (snoring, sleep apnea) or other relevant diseases. A review of systems, previous hospital admissions, and relevant family history is also noteworthy. The record should indicate any history of allergies or adverse drug reactions, medications used prior to sedation, and the patient's last oral intake [8, 11].

Document a careful physical exam with a focus on the patient's airway and cardiovascular system. Record the patient's correct weight, *in kg only*. Of course, it is important to record vital signs and oxygen saturation at specific intervals [8, 11].

A time-based record should include all drugs and doses administered and the routes of administration. It should include at least the patient's name, route, site, time of medication, dosage, and effect of the administered drugs on the patient. Certainly, any adverse effects should be recorded. Record findings while monitoring the patient, such as oxygen saturation. Document the child's level of consciousness during the procedure, e.g., how he/she responds to verbal commands or tactile stimulation [8, 11].

Prior to the patient's discharge from the sedation unit, document the child's level of consciousness and oral intake. Discharge instructions may be preprinted and must be reviewed with the child's guardian before the patient is allowed to go home. Include a reminder to parents in the discharge instructions that the child should not be involved in play that requires coordination such as bike riding or skating for perhaps 24 h. Recommend adult supervision at home. Unsupervised bathing, use of electrical devices, or other possibly dangerous items should not be permitted for at least 8 h. The family should be told who and when to call if there are questions or concerns. Provide a 24-h telephone number to call if any questions. Discuss safe transport home with the patient's guardian [8, 11].

Never Alter Medical Records

It is never wise to alter a patient's medical record or make a late entry after an adverse event has occurred. Appropriately correct errors in charting with a single line placed through the error; date and initial the correction. Do not attempt to cover up the mistake by blacking out words or phrases, as this will likely arouse suspicion. Should litigation ensue, it is usually easier to defend missing facts or a poor record than one that has been altered [31].

Managing Medical Errors

When a complication related to sedation occurs, a full investigation is needed. For hospital-related events, contact the hospital's Risk Management office. This office is the division of the hospital that manages adverse outcomes and attempts to prevent them by careful monitoring of hospital "systems." Risk Managers will generally guide the staff about documentation of the event and any further action that is necessary. Subsequent treatment rendered to the patient should be noted in the medical record. Some recommend that lengthy details of the problem should not be discussed in the record, but rather documented in an Incident Report. The Incident Report should be written as soon after the adverse event as possible, and the hospital Risk Management Office should receive the only copy. The Incident Report should contain a description of the incident, names, date,

time of the event, clinical impact of the problem, and actions taken. Incident Reports are often discoverable. Do not include a written apology or conclusion assigning blame to an individual. It is also unwise to make self-serving or defensive statements in the medical record [32].

When an error has occurred, full disclosure to the family is usually recommended. Offering a sincere apology to the family often diffuses anger. Studies have shown families are more likely to sue if they believe the doctor concealed the truth. Disclosure allows a good doctor–patient relationship to continue and thus reduces risk. Families often seek advice from a lawyer to get information about what happened to their child. Open communication after an error may prevent the need to seek legal advice [33, 34].

When to Contact an Attorney

Whenever a medical error has occurred, or in the event of a bad outcome (even if no error took place), it is wise to contact the hospital Risk Management Office and give them a "heads up" notification of a potential legal problem. In some cases, the physician is not expecting a lawsuit, but may receive written notification of legal action, known as a "complaint." This complaint should be taken seriously. Even if you disagree with everything in the complaint (charges are often exaggerated), *do not ignore this*. The complaint may list statements that are demoralizing or insulting, but they are only unproven accusations.

Notify your hospital Risk Manager as soon as you receive the complaint. Also, notify your malpractice insurance company and make certain that a defense attorney will be assigned. Your attorney, once assigned to the case, will discuss the matter with you and send an "Answer" to the complaint (generally denying the allegations) within a certain time frame [6]. The clinician has a right to hire a "private" attorney to represent him or her, but this is usually at the clinician's expense, and is rarely done. Some clinicians will hire a private attorney in rare cases when the insurance company wishes to settle the case, and the clinician disagrees with this decision.

If you are named in a malpractice lawsuit, do not panic! Being named in a malpractice lawsuit does not mean you are a "bad" clinician. It does not necessarily mean you have done anything wrong. Tell your attorney all you know about the incident and help him/her develop the case. Make some recommendations for a possible expert witness for your defense. Do not discuss the case with colleagues. Do not call the patient's family to discuss the matter [6].

Quality Improvement

The Joint Commission requires each facility to perform quality improvement review of sedation practices. Each facility should track adverse events, such as the need for airway intervention, apnea, desaturation, and prolonged or unsatisfactory sedation. These events should be examined to detect system flaws, and to reduce risk in the future [8, 11].

Family Member Presence for Procedures

No studies have been done to evaluate the effects of family member presence during sedation and procedures on litigation. However, studies show that most family members who witness a procedure report favorable opinions of the process. This favorable opinion by families holds true for resuscitation, even when the patient dies. In one study, 94% of family members surveyed stated that they would participate again if given the opportunity, and 76% believed they adjusted better to the death of a relative by witnessing the resuscitation [35]. Thus, little information in the literature supports the belief that family member presence during sedation and procedures will increase legal risks for a clinician. Parent satisfaction may actually improve if they are present for a procedure

involving sedation and the likelihood of a lawsuit may decrease, as satisfied family members are generally less likely to file a lawsuit [35, 36].

Conclusion

Healthcare Costs and the Medical Liability System

The implications of the medical liability system in the United States are significant. As President Obama pushes for healthcare reform, the public is becoming increasingly aware of the expenditure related to medical liability. In 2004, the Congressional Budget Office estimated that malpractice costs, excluding defensive medicine, accounts for less than 2% of healthcare spending [37]. Defensive medicine, however, is a significant expense, reflecting the physician's purposeful overuse of the healthcare system in order to protect themselves from liability. A recent publication looked at the total costs of the medical liability system, accounting for all expenses that could be quantified and expressed. The costs were put into categories: indemnity payments (cost to the malpractice defendant and their insurer as well as the payout to the plaintiff), administrative costs (attorneys etc.), defensive medicine costs, and other costs [38] (Table 21.3). It is estimated that the cost of a defense attorney averages 19¢ per indemnity dollar [39]. Other costs include expenses such as the risk management offices and fees spent by the hospitals, an estimate which in 2008 averages from $185,000 to $1.9 million per hospital – totaling a conservative estimate of $1.06 billion dollars annually for the 5,708 registered hospitals in the United States [38]. In total, the annual expenditure related to medical liability in the United States has been estimated at $55.6 billion (Table 21.3). This reflects by 2008 standards, 2.4% of national healthcare spending [38]. Thus, as physicians work

Table 21.3 Estimates of national costs of the medical liability system

Component	Estimated cost (billions of 2008 dollars)	Quality of evidence supporting cost estimate
Indemnity payments	$5.72	Good as to the total moderate as to the precision of the split among the components
Economic damages	$3.15	
Noneconomic damages	$2.40	
Punitive damages	$0.17	
Administrative expenses	$4.13[a]	Moderate
Plaintiff legal expenses	$2.00[a]	Good
Defendant legal expenses	$1.09	Moderate
Other overhead expenses	$3.04	Good
Defensive medicine costs	$45.59	Low
Hospital services	$38.79	
Physician/clinical services	$6.80	
Other costs		
Lost clinician work time	$0.20	Moderate
Price effects	–[b]	Low
Reputation/emotional harm	–[b]	No evidence
Total	$55.64	

Source: Copyrighted and published by PROJECT HOPE/*Health Affairs* as Mello et al. [38]. The published article is archived and available online at www.healthaffairs.org

[a] Although plaintiff legal expenses are separately itemized, they are not included in the overall administrative costs because, in the contingent fee system, they are already represented in the indemnity costs

[b] These costs are not estimable with the available data

toward decreasing their liability, creating safety measures to improve outcome and reduce adverse occurrences, it is the responsibility of all in our society to recognize that we all share in the burden of medical liability.

Summary

The majority of children who receive sedation and analgesia outside the Operating Room have a good outcome, and benefit from efforts to reduce pain and anxiety during a procedure. Occasionally, there is a preventable or unavoidable complication. Those providing care to sedated children must take steps in advance of a procedure and vigilantly monitor the child during a procedure in order to minimize potential adverse outcomes. Develop and follow policies to guide care. Act reasonably. Provide high quality care and be prepared to rescue a patient if there is an adverse event. Communicate well with patients, families, and staff. Document the good care delivered to help defend any litigation (Table 21.4).

Table 21.4 Preventing malpractice lawsuits related to sedation

Practice "good medicine"
Take precautions to prevent adverse outcomes
Ask for help when needed
Communicate well
Listen to family members and keep them informed
Speak in terms the family can understand
Develop a sense of trust with the family
Communicate carefully with other staff members
Be cautious during patient handoffs
Document carefully
Use a well-designed, time-based record
Keep the medical record neat and professional in appearance
Indicate that information previously obtained was reviewed
Never alter the medical record after discharge of the patient
Correct errors appropriately
Provide written discharge instructions
Document that these were reviewed verbally
Manage errors appropriately
Follow hospital policies
Contact Risk Management Office
Do not attempt to cover up
Investigate errors thoroughly
Disclose errors to families
Apologize when appropriate

Case Studies

Case 1

A 2-year-old boy was brought to an Illinois medical center by his mother to check a "bump on his head," sustained when he fell down some stairs at a family birthday party. A CT scan was performed several hours after the boy entered the hospital, and it was reported to be normal. After the test was completed, the child stopped breathing, allegedly as a result of an overdose of sedative medication administered for the CT scan. Although he was revived in the hospital emergency department, he suffered irreversible brain damage. Five days later he was disconnected from a respirator and died. An autopsy by the Medical Examiner's office found that he died from a sedative overdose.

The family sued the hospital and this resulted in a $3,000,000 settlement, including $2,000,000 from the hospital and $1,000,000 from an individual insurance policy held by a registered nurse who had given the sedative [40].

Teaching point – this case reminds us that giving sedation even for a "simple procedure" such as a CT scan adds significant risk. The child who receives sedation must be carefully monitored by staff who know the effects and side effects of the drugs used. Plans to rescue the patient must be in place, in the event of an apneic episode.

Case 2

A 4-year-old boy presented to a Michigan hospital for an MRI to evaluate a leg mass. He

was given midazolam, fentanyl, and pentobarbital prior to the MRI. The patient suffered a cardiopulmonary arrest during the MRI. He was left with permanent central nervous system damage, resulting in cerebral palsy and mental retardation. The family sued and alleged that inappropriate amounts of medication were utilized. They also alleged that the hospital staff failed to monitor the patient and failed to insure appropriate oxygen delivery. They believed that his permanent and severe brain injuries were a result of the incident. The defendant hospital contended that the child was unusually sensitive to the medications and was appropriately monitored. The case was settled for $2,950,000 [41].

Teaching point – While details are unavailable, one has to question whether the patient in this case was appropriately monitored. One should also question the use of fentanyl for a painless procedure such as a MRI. Sedation may have been desirable, but a narcotic analgesic seems unnecessary and perhaps dangerous in this case. The clinician should have a clear understanding of the goals of sedation and then use the drugs wisely [10]. Also, decide whether deep sedation or just anxiolysis is needed.

Case 3

A 2-year-old boy was brought to a Texas ED for treatment of a tongue laceration that he suffered while playing. The boy was given midazolam and morphine for sedation to repair the laceration. Naloxone was given later. The patient was discharged from the ED 8 h after the procedure, apparently still asleep. He never woke up at home, and was later pronounced dead. The parents sued the hospital and the treating physician, claiming that the medication was given inappropriately and the child was not properly monitored. The hospital settled the case for $975,000 [42].

Teaching point – Premature discharge of a sedated patient from the ED can have disastrous consequences. Before discharge, the child should have normal cardiovascular function, an intact gag reflex, and a patent airway. The state of hydration should also be adequate. The child should be easily aroused and able to sit and talk, if age appropriate. Younger children or those with neurologic dysfunction should be close to their presedation level of function before discharge [8].

Case 4

In September 2002, an adult patient with Crohn's disease arrived at a Minnesota hospital for his scheduled iron infusion. He required premedication because he had developed hives with the iron transfusion in the past. He was given 50 mg of diphenhydramine intravenously, along with 100 mg of steroids and 2 mg of lorazepam orally. Despite premedication he developed a reaction when iron was infused and was given an additional 50 mg of diphenhydramine and 2 mg of lorazepam intravenously. The patient was released without a responsible adult to pick him up. Fifteen minutes after leaving the hospital parking lot, the patient's car rolled over at high speed in a single vehicle crash. He suffered catastrophic head injuries and died. The state trooper who investigated the crash concluded that the patient fell asleep while driving.

The family sued the hospital that administered the sedatives. During discovery it was learned that the nurses who gave the medications were not familiar with the drugs or their actions. The family believed the nurses were negligent for failing to make certain the patient was discharged to a responsible adult. The case was settled before trial for $2.35 million [43].

Teaching point – Medical personnel caring for the sedated patient must be familiar with the drugs that are given and their actions. The patient must be carefully monitored until back to baseline. A pediatric patient (teenager) should not be permitted to drive home alone after receiving sedation for

a procedure. Since it is difficult for a parent to care for her child while driving, one should consider prolonged observation at the medical center if the only adult present has to drive the car [8].

Case 5

A 15-year-old boy underwent surgery at a hospital in Utah in April 2004 to relieve chronic nasal obstruction, deviated septum, and turbinate hypertrophy. He was given 50 mg of morphine during surgery. An additional 75 mg of intravenous meperidine was administered while he was in the Recovery Room after surgery. The patient was still sleeping 2 h after the surgery. At that time, the parents were allegedly told that the patient "had to leave." The parents helped the patient to get dressed and he was awake long enough to get into their car. At home he slept on the couch while his parents took care of other things. When the parents checked on him, he was found with no pulse or respiration. Paramedics were called to the scene and the patient was transported by ambulance to a hospital where he was declared dead.

The family sued and claimed that the patient should not have been discharged, as he did not meet discharge criteria. The coroner opined that the postmortem level of meperidine in the patient's blood suggested that he had taken more of this medication after discharge from the hospital. The parents denied this and claimed that the boy had refused an additional dose of the medication offered by a nurse before leaving the hospital. The family argued that the coroner failed to take into account postmortem redistribution of drug levels.

A confidential settlement was reached [44].

Teaching point – This was a preventable death, and the case would have been difficult to defend in court. The patient apparently received a large quantity of narcotics and the hospital was responsible for monitoring him until safe discharge was possible. It is not known if the patient was carefully evaluated before discharge or what documentation existed as to his condition. The closing of a Day Medicine Unit or Recovery Room (implied but not confirmed in this case) does not justify early discharge of a patient who is recovering from sedation or anesthesia [44].

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Designing a Safe and Reliable Sedation Service: Adopting a Safety Culture

22

Paul R. Barach

Background

While millions of children receive sedation every day, high-profile cases have brought medical errors in pediatric sedation to the public's attention. Children of all ages feel pain and experience anxiety. Alleviating pain and anxiety in children is a key component during the care provided to hospitalized and ambulatory children. While reassurance, parental presence, distraction, and behavioral strategies may offer relief, pharmacologic intervention is often required, especially in the acute-care setting. Sedation for children in the operating room and increasingly outside the operating rooms has been a growing industry. This growth is attributed to the proliferation in the volume and type of procedures outside the operating room, an increase in the demand for special conditions to produce better imaging and diagnostic results (i.e., MRI and dentistry), and an increase in the complexity of cases due to an increase in survival rates of children with complex pathology.

A clinical microsystem is a group of clinicians and staff working together with a shared clinical purpose to provide care for a population of patients. The clinical purpose of pediatric sedation and its setting define the essential components of the microsystem which include the clinicians and support staff, information and technology, the specific care processes, and the comptencies that are required to provide care to its patients. Examples of clinical microsystems include a cardiovascular surgical care team, a community-based outpatient care center, a neonatal intensive care unit, and a pediatric sedation service. The clinical microsystem provides a conceptual and practical framework for approaching organizational learning and delivery of safe care in pediatric sedation. To understand the functioning of these healthcare microsystems, and to improve perioperative patient safety and reliability in children, it is necessary to study the components that make up the system – humans, technologies, and their complex interactions. In health care, the premium placed on practitioner autonomy, the drive for productivity, and the economics of the system may lead to severe safety constraints and adverse medical events.

Adequate pain control and sedation ensure the comfort, and cooperation of the child, influences the success of the procedure and can affect the child's future attitudes toward healthcare providers and medical care. This chapter describes key developments in safety and reliability over the last several years – safety research, risk and reliability management approaches, the role of human factors and organizational practice models.

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Introduction

Safety Within the Context of Systems Thinking

Medical care itself has the potential to cause harm [1]. However, general acknowledgment that much iatrogenic injury may be due to preventable human error or system failure appears to have been slow. While medical errors have existed since before Hippocrates, the true magnitude of adverse events in health care was brought to the forefront of public debate after the Institute of Medicine (IOM) reported in 1999 that approximately 44,000–98,000 deaths per year were attributable to errors in hospital care [2]. Simply being hospitalized, on average, carries a 200-fold greater risk of dying from the care process than being in traffic, and a 2,000-fold greater risk than working in a chemical industry, or flying on a commerical flight [3, 4]. Patient safety is now a defined priority nationally and internationally, at the World Health Organization (WHO), as a key public health and quality improvement policy.

The elective and emergency use of sedative agents in the pediatric population has readily expanded with several excellent reviews [5]. The clinical microsystem in the perioperative setting provides a conceptual and practical framework for simplifying how sedation is delivered and how to deliver it safely with no harm [6, 7]. Previous research on clinical microsystems has identified 10 success factors, as summarized and defined in Table 22.1 [82].

The microsystem construct allows one to invest safety and quality into these subsystem elements that are less dependent on the presence of a particular individual but on a process that performs in a more predictable and robust fashion [8]. Achieving high reliability requires a capacity to recognize unnecessary variability and the capability to reduce it either through process redesign or standardization [9]. While this is often done through "work arounds" which are designed to "fix" a specific problem at the time it arises, it does not allow for a deeper consideration of the source of variability to avoid when faced with the same problem in the future [10].

Table 22.1 Characteristics of high-performing sedation microsystems

Microsystem characteristic	Definition
Leadership	The role of clinical leaders is to balance setting and reaching collective goals, and to empower individual provider autonomy and accountability, respectful action, and reflection
Organizational support	The hospital looks for ways to support the work of the sedation service and helps to coordinate the handoffs between other clinical microsystems (i.e., PACU, ICU, etc.)
Staff focus	There is selective hiring of the right kind of people. The orientation process is designed to fully integrate new staff into a safety culture
Education and training	All clinical microsystems have responsibility for the ongoing education and training of staff including simulation and team training
Interdependence	The interaction of staff is characterized by trust, collaboration, willingness to help each other, appreciation of complementary roles, respect, and recognition that contribute to a shared purpose of safer and high-quality pediatric care
Patient focus	The primary concern is to meet all patient and parent needs – caring, listening, educating, and responding to special requests, innovating to meet patient needs, and service flow
Community focus	The microsystem is a resource for the community and ensures all care is about enhancing community well being
Performance results	Performance focuses on patient outcomes, avoidable costs, streamlining delivery, using data feedback, reducing variation, and encouraging frank discussions about performance
Process improvement	An atmosphere for learning and redesign is supported by the continuous monitoring of care, use of trigger tools and benchmarking, and staff who are empowered to innovate
Information technology	Information is the connector – staff to patients, staff to staff, needs with actions to meet needs. IT facilitates effective communication, and multiple formal and informal channels are used to keep everyone informed all the time

Source: Adapted from Barach and Johnson [82]. Reprinted with permission from BJM Publishing

Human Error and Performance Limitations

Although there was little research in the field of healthcare safety until the mid-1980s, in other fields (e.g., aviation, road and rail travel, nuclear power, chemical processing) the field of safety, science, human error and the intensive accident investigations have been well developed for several decades [11, 12]. The rapidly rising rate of litigation in the 1980's, and increasing interest from the media, brought medical accidents to the attention of both doctors and the general public. In parallel with these changes, researchers from several disciplines developed methods for the analysis of accidents of all kinds [13].

Theories of error and accident causation and high reliability theory have evolved that are applicable across many human activities although they have not as yet been widely used in medicine [14]. These developments have led to a much broader understanding of accident causation, with less focus on the individual who makes an error, and more on preexisting organizational and system factors that provide the context that enables errors to occur. An important consequence of this has been the realization that the accident analysis may reveal deep-rooted, unsafe features of organizations. Reason's "Swiss cheese" model captures these relationships very well [15] (Fig. 22.1). Understanding and predicting safe sedation performance in ambulatory, emergency department or perioperative room settings requires a detailed understanding of both the setting and the human factors that influence the performance and outcomes of the pediatric sedation team.

Standardized Definitions and Patient Safety Taxonomy

Patient safety monitoring and reporting systems are intended to act as surveillance systems that identify adverse events and provide early warnings of potential failure. For this monitoring or reporting system to be effective, it must be based on an accepted and standardized classification. In this emerging field of study, many different definitions are used and a common terminology has yet to emerge leading to confusion. Iatrogenic injury means injury originating from or caused by a physician (*iatros*, Greek for "physician") [16]. However, the term has come to have a broader meaning, and is now generally considered to include unintended or unnecessary harm or suffering arising from any aspect of healthcare management [17]. The lack of an accepted standardized nomenclature for medical errors complicates the development of a response to the issues outlined in the IOM report, and makes comparison of different studies and reports problematic [18]. Error is defined as "the failure of a planned action to be completed as intended (i.e., error of execution) or the use of a wrong plan to achieve an aim (i.e., error of planning)" [16, 17]. It may occur anywhere along the patient care continuum, but may

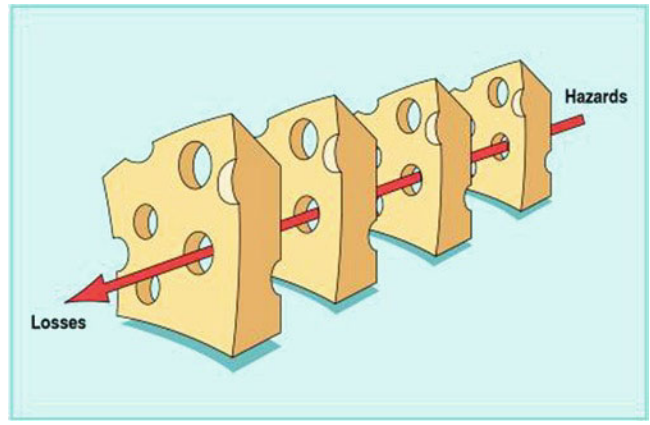

Fig. 22.1 The Swiss cheese model of how defences, barriers, and safeguards may be penetrated by an accident trajectory (reproduced from Reason [113], with permission from BJM Publishing)

not always result in harm or injury. An error which is intercepted before reaching the patient, or which reaches the patient but does not cause harm, is known as a "near miss" or "close call" [18].

Reporting Systems

A comprehensive effort to record and analyze related data from these events in health care has, however, lagged other industries (e.g., aviation, nuclear power industry) [19].

The definition of Sentinel Events is more straightforward than that of "near miss" events. In April, 1998 the Joint Commission approved the Sentinel Event Policy which encourages reporting of Sentinel Events as those which affect recipients of care (patients, clients, residents) and that resulted in an unanticipated death or major permanent loss of function, not related to the natural course of the patient's illness or underlying condition [20]. The reporting of "near miss" events is more difficult to capture than that of adverse events. The benefits of "near miss" reporting offer the advantage of identifying an adverse event which may have occurred. A "near miss" represents the opportunity to identify a potential safety problem which could have resulted in a significant injury [21].

Reason's "Swiss cheese" model is an accepted model, which identifies multiple errors within a system as cascading into an adverse event [15]. At autopsy, up to 40% of patients have been identified as having medical errors which contributed to death [22–24]. Studies in the intensive care unit report an average of 1.7 errors per day per patient of which 29% were "near miss" events, with the potential for serious or fatal injury [25]. Neither voluntary reporting nor mandatory enquiry captures all adverse events. Voluntary reporting detected 166 (32%) adverse events among 100 patients, of which 119 were undetected by mandatory reporting. Forty-nine events (9%) were detected by both methods. The number and severity of events reported by the two methods were significantly different. While the two methods both capture some events, mandatory reporting captures serious events, while voluntary reporting captures mainly insignificant and minor events [26].

The ability to identify "near miss" events and determine a root cause which could avoid future Sentinel events is important for all medical environments and is one which will be explored for pediatric sedation.

Three Universal Ingredients of Accidents

There are three reasons why adverse events occur during pediatric sedation. (1) *All human beings, regardless of their skills, abilities, and specialist training, make fallible decisions and commit unsafe acts*. This human propensity for committing errors and violating safety procedures during sedation can be moderated by selection, training, well-designed equipment, and good management, but it can never be entirely eliminated. (2) No matter how well designed, constructed, operated, and maintained they may be, *all man-made systems possess latent failures to some degree*. These unseen failures are analogous to resident pathogens in the human body that combine with local triggering factors (i.e., life stress, toxic chemicals, etc.) to overcome the immune system and produce disease. (3) *All human endeavors involve some measure of risk*. In many cases, the local hazards in complex socio-technical systems are well understood and can be guarded against by a variety of technical or procedural countermeasures. These three ubiquitous accident ingredients reveal something important about the nature of making care safer [27, 28]. We can mitigate the risk of adverse events during sedation of children and increase its reliability by process improvement, standardization, and an in-depth understanding of the safety degrades in systems. We cannot, however, prevent all risk.

The Organizational Accident

The accidents and adverse events that still occur within systems which possess a wide variety of technical and procedural safeguards (e.g., fire in the operating room, wrong patient procedure), have been termed organizational accidents [14, 28]. These are mishaps that arise not from single errors or isolated component breakdowns, but from the insidious accumulation of delayed action failures

lying mainly within the managerial and organizational spheres. Such latent failures, as we see often in analyzing pediatric sedation mishaps, may subsequently combine with active failures and local triggering factors by clincians, to penetrate or bypass the system defenses. The etiology of an organizational accident can be divided into five phases [28]:

1. Organizational processes giving rise to latent failures;
2. Error and violation producing conditions within workplaces (operating room, pharmacy, intensive care units, etc.);
3. The commission of errors and violations by "sharp end" individuals (clinicians);
4. Breaching of defenses or safeguards; and,
5. Outcomes that vary from a "free lesson" to a catastrophe.

The unsafe acts of those in direct contact with the patient are the end result of a long chain of events that originate higher up in the organization at the management level. One of the basic principles of error management is that the transitory mental states associated with error production – momentary inattention, distraction, preoccupation, forgetting – are the least manageable links in the error chain because they are both unintended and largely unpredictable [29]. These errors have their cognitive origins in highly adaptive mental processes [30]. Such states can strike healthcare providers at any time.

Applying Human Factors in the Clinical Environment

The study of human factors is an integral part of current safety research [31]. Human Factors (also called *ergonomics*) is the study of human interactions with tools, devices, and systems with the goal of enhancing safety, efficiency, and user satisfaction [32]. Human error in medicine can range from medication errors while selecting and loading a medication syringe to errors while recovering the patient after sedation. Knowledge about how people interact with each other and with technology has been productively applied to enhance human performance in a wide range of domains, from fighter planes, to kitchens, to operating rooms to emergency departments. One must carefully consider the impact of the many "performance shaping factors" that are known to play a role in optimizing sedation (see Table 22.2) [33, 34]. However, even though most error can be traced to action (or inaction) of an individual, the root causes of error go beyond a single individual [35].

Table 22.2 Examples of performance shaping factors affecting sedation care

Individual factors
Clinician knowledge, skills, and abilities
Cognitive biases
Risk preference
State of health
Fatigue (including sleep deprivation, circadian effects)
Breaks and boredom
Substance use/abuse (e.g., alcohol hangover effects)
Other stressors
Personality factors
Task factors
Task distribution
Task demands
Workload
Job burnout
Shift work
Team/communication
Teamwork/team dynamics
Interpersonal communication (clinician–clinician, clinician–patient)
Interpersonal influence
Groupthink
Environment of care
Noise
Lighting
Temperature and humidity
Motion and vibration
Physical constraints (e.g., crowding)
Distractions
Equipment/tools
Device usability
Alarms and warnings (alarm fatigue)
Automation
Maintenance and obsolescence
Protective gear
Organizational/cultural
Production pressure
Culture of safety (vs. toxicity)
Policies
Procedures
Documentation requirements
Staffing
Cross coverage
Hierarchical structure
Reimbursement policies
Training programs

Factors that influence the pediatric sedation microsystem's effectiveness include the performance of individual team members, the equipment they use, the care environment (e.g., established care process and procedures), and the underlying organizational and cultural factors. For example, distractors such as information overload, noise, key team absence can be a danger to both patient and healthcare professionals. Fear of reprisal and punitive culture can greatly diminish error reporting and learning. Research on Patient Safety Human Factors has expanded to study team interaction and collaborative decision-making [36], the interaction of humans and technology [37], the importance of technology and alarms [38], organizational issues [39], institutional functions, and national regulations.

Fatigue and Its Impact on Human Performance

There is extensive literature on the adverse effects of sleep deprivation and fatigue on individual clinician performance [40–42]. A series of studies have demonstrated that physicians-in-training who work traditional marathon shifts of 24–30 consecutive hours [43]:

- Make 36% more objectively documented serious medical errors in the care of critically ill patients;
- Make 5 times as many serious diagnostic errors;
- Have twice as many physiologically documented attentional failures during night work;
- Suffer twice as many motor vehicle crashes on the drive home from work;
- Inflict 61% more sharp injuries on themselves than physicians-in-training working regular day shifts; and,
- By self-report, make 700% more fatigue-related serious errors in patient care that harm patients, including 400% more errors that lead to their patients' deaths when working more than five marathon shifts in a month.

Results of these studies and others have led to work-hour limits for clinicians in training but even after work-hour rules: 30 h consecutive shifts are still the norm in training programs [44]. Sleep loss is associated with reduced performance on tasks requiring vigilance (such as monitoring alarms), cognitive skills, verbal processing, manual dexterity, and complex problem-solving [45]. Performance decrements begin with a lack of appreciation of the skills being degraded, and accumulate with chronic partial sleep deprivation. Reducing healthcare worker fatigue was recognized as a goal for 2009 by The Joint Commission. Recognizing the risks of fatigue, government regulatory bodies around the world have established consecutive work limits of 8–11 h for pilots, truckers, and healthcare providers [46].

The Role of Technology in Sedation

Technology plays both active and passive roles in pediatric sedation. The active role is reflected in functions like error detection (alerts and reminders) [47], information processing, and data mining. The passive role of information technology (IT) is exemplified by how it facilitates communication, eases workflow, and distributes information effectively and efficiently. It also serves as an important cognitive tool that enhances and aids decision-making [48]. The passive role of technology in facilitating patient safety is more indirect and yet may be more important in that it strengthens and assists processes integral to patient safety, thus enhancing the resilience of the system [49]. Health care is being driven by technology, and pediatric proceduralist providers are at the forefront of this drive. Recent studies have highlighted the confusion caused by infusion pumps [50], ventilators [51], and spinal cord implant pumps [52], in which poor interface design, complex navigation menus, and lack of clinical feedback to users contribute to unreliable and hard to operate medical devices. These technologies already have had individual and collective effects on some aspects of medicine and their influence is increasing [53, 54].

Infusion pumps, for example, use audible alarm signals (AAS) to announce the occurrence of nonroutine events that could lead to harm and alarm fatigue [55]. Investigations into the performance of AAS revealed that the problems associated with their performance include,

urgency-mismatch and lack of standardization [56]. In our psychoacoustics lab, we found that there was large variation among providers in their responses to urgency signals [57]. A standard method for testing usability does not exist. Challenges in prioritizing alarm signals will remain a barrier to safe and effective monitoring of patients as care environments get more complex and more parameters are monitored. Careful and selective automation is needed due to the dangers and the unintended consequences of implementing new technologies that are not ergonomically sound [58, 59].

Engineering a Culture of Safety

National cultures arise largely out of shared norms and values, while an organizational culture is shaped mainly by shared practices. How do we create an optimal organizational climate that fosters safe sedation outcomes? Culture can be defined as the collection of individual and group values, attitudes, and practices that guide the behavior of group members [60]. Acquiring a safety culture is a process of collective learning and mindfulness that recognizes the inevitability of error and proactively seeks to identify latent threats. Characteristics of a strong safety culture include a commitment of the leadership to discuss and learn from errors, communications founded on mutual trust and respect, shared perceptions of the importance of safety, encouraging and practicing teamwork, and incorporating non-punitive systems for reporting and analyzing near miss and adverse events [61]. There is a long tradition in medicine of examining past practices to understand how things might have been done differently.

Engineering a safety culture requires a process of collective learning and trust building. When the usual reaction to an adverse incident is "Write another policy" and "more training," this does not make the system more resistant to future organizational accidents, but it may deflect the blame from the organization as a whole. However, morbidity and mortality conferences, grand rounds, and peer review share many of the same shortcomings [62]:

1. A lack of human factors and systems thinking;
2. A narrow focus on individual performance, excluding analysis of contributory team factors and larger social issues;
3. Retrospective bias; a tendency to search for errors as opposed to the myriad causes of error induction; and,
4. A lack of multidisciplinary integration of findings and lessons into an organization-wide safety culture, thus perpetuating a "code of silence" and recurrence of similar events.

If *sharp end* clinicians who deliver sedation are not empowered by managerial leadership to be honest and reflective on their practice, rules and regulations will have a limited impact on enabling safer outcomes. Healthcare administrators need to understand the fundamental dynamics that lead to adverse events. Employing tools such as root cause analysis (RCA), and failure mode and effects analysis (FMEA) can help clinicians and others better understand how adverse events occur. These totals can lead to resilience only if the culture is receptive [19].

Medication Errors

Medication harm to children occurs at relatively high frequency due to several inherent risk factors (see Table 22.3).

Medication errors have been the most extensively investigated realm in patient safety because of a number of factors. Medication errors may be classified along the medication-use continuum into prescribing, dispensing, and administration errors. Common factors contributing to harm in all three stages is the use of error-prone abbreviations, dose expressions,

Table 22.3 Special issues for children relevant to medication safety

Weight-based dosing (and weights change frequently)
Organ system development is variable, affecting metabolizing and excretion
Medicines mixed by pharmacists or nurses at time of use
Pediatric medicines often need to be diluted from adult formulations
Many pediatric medications come in multiple formulations

Table 22.4 Common errors made in pediatric sedation and analgesia

Failure to fully evaluate the child prior to administration of pharmacologic agents
Administration of drugs to a child with a full stomach
Lack of appropriate monitoring
Incorrect use of two or more drugs (polypharmacy)
Lack of knowledge concerning the pharmacodynamics and pharmacokinetics of the drugs being used

Source: Data from [91]

symbols, drug abbreviations, and stems [17, 38] (see Table 22.4).

According to Phillips et al., the number of outpatient visits in the United States increased by 75%, whereas the number of inpatient days decreased by 21% between 1983 and 1993; outpatient deaths related to adverse drug errors (ADE) increased 8.48-fold during this 10-year period, as compared to a 2.37-fold increase for inpatient deaths [63].

In 1995, Bates et al. found 334 errors led to 264 ADEs. The main reasons for the ADEs are as follows: (a) lack of knowledge of drug (29%); (b) lack of patient information (18%); (c) rule violation (10%); (d) slips and memory lapses; (e) transcription errors; (f) faulty check and balance systems; (g) and communication among services [64]. Woods found that there were 2.3–11 ADE per 100 pediatric admissions [65]. Kausahl et al. in 2001 noted that there were ten potential ADE per/100 children admissions, with 22–60% of ADEs preventable. [66]. Takata et al. showed using a drug trigger tool that the average ADEs occur 2.03 time/per child and patients who had adverse events had a chance of 3.27 ADE's per admission [67]. Opiates caused 51% of ADEs, with most harm occurring at the ordering and administration stages. 17% of all harm in the PICU setting was drug related.

Malviya et al. found that sedation of children by nonanesthesiologists had a 20% adverse event rate with over 5.5% suffering oxygen desaturation less than 90% [68]. Children with underlying medical conditions (ASA > 3) and those who are very young (<1 year) are at increased risk of adverse events, which indicates that a greater degree of vigilance may be required when these patients require sedation.

Cote et al. found that all sedative drugs suppress the CNS with respiratory depression being the most significant adverse effect following sedative drug administration [69]. Cote et al. found 60 deaths with permanent CNS injury with 80% of events related to a respiratory event. Poor outcome was associated with: >3 drugs used; inadequate resuscitation (outpatient > inpatient); inadequate monitoring, particularly SpO_2; inadequate initial evaluation; and inadequate recovery phase. Impaired airway control was the single most serious adverse event leading to hypoventilation in which mild sedation leads to general anesthesia.

Anesthesiology as a Model for Pediatric Sedation

The field of Anesthesiology is a celebrated example in health care, in which an organized and continuous effort over a period of 20 years has led to major improvement in patient safety and system reliability [70]. The safety of anesthetic procedures has improved up to an estimated tenfold in the last 30 years (from 2 deaths/per 10,000 to 1 death/per 300,000 patients) [71]. Many feel that the overall approach in the field of Anesthesiology has led to a 100-fold safer profile than the rest of health care (see Fig. 22.2). The tools routinely deployed to make anesthesia safer include enterpise risk management team training [72], simulation [73], incident reporting [74], and safety systems training [14]. The pediatric perioperative cardiac arrest (POCA) registry is ground breaking in its ability to collaboratively learn about rare events such as respiratory failures and has led to changing practices around Halothane use [74, 75].

Patient Handoffs

The nature of pediatric sedation can require several handoffs (or handovers) of kids leading to potential loss of vital information and potential harm [76, 77]. Much can be learned from other high-risk industries that have been engaged in studying and improving handoffs. From direct observations at the National Aeronautics and Space Agency,

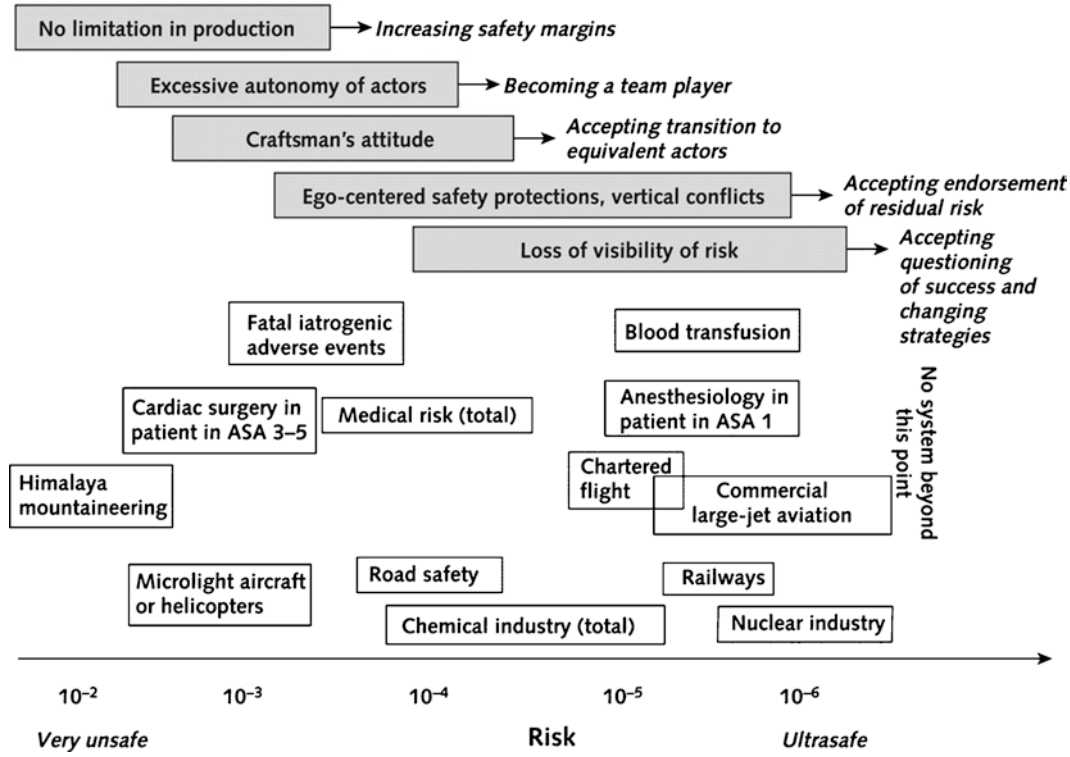

Fig. 22.2 Average rate per exposure of catastrophes and associated death associated with deaths in various industries and human activities. System challenges in gray boxes, postential solutions identified by arrows (reprinted with permission from Amalberti et al. [9])

nuclear power plants, and transportation dispatch centers, a framework of strategies for handoffs has emerged [77, 78]. Certain strategies, such as mapping the process of care, standardization of questions and face-to-face verbal updates, resonate directly with maximizing reliable handoffs. These processes are supported by evidence and expert opinion as best practices associated with improved handoff communication [79–81]. Functional system mapping is based on a comprehensive task analysis which takes into consideration the sub and supra-system elements that allow the microsystem to function, as shown in [82].

Designing a Safe Sedation Service

Safe sedation requires coordinated teamwork, a learning culture and trust among the team members. The role of effective teamwork in repeatedly accomplishing complex tasks safely is well accepted in many domains [83]. Teamwork during sedation care can be characterized in a number of different ways, and multiple deficiencies may interact to impair team success and patient outcomes (see Table 22.5) [84, 85]. The team evaluation must include the review of the secondary management including careful delineation of team structure and planning, on-going team training, effective support structures, and continuous feedback and quality improvement based on practice and immersive learning opportunities [35]. Valuable tools for training the sedation team include the use of simulation [86], standardized patients, and videotape-based analysis and debriefing [87].

Sedation teams seem to make fewer mistakes than do individuals, especially when each team member knows both his responsibilities and those of the other team members. However, simply bringing individuals together to perform

Table 22.5 Problems and pitfalls in pediatric sedation teamwork

Difficulties coordinating conflicting actions
Poor communication among team members
Failure of members to function as part of a team
Reluctance to question the leader or more senior team members
Failure to prioritize task demands
Conflicting occupational cultures
Failure to establish and maintain clear roles and goals
Absence of experienced team members
Inadequate number of dedicated sedation team members
Failure to establish and maintain consistent supportive organizational infrastructure
Leaders without "the right stuff"

Source: adapted and reprinted with permission from Barach et al. [114]

sedation on a child does not automatically ensure that they will function as a team. A safe pediatric sedation team depends on a willingness of clinicians from diverse backgrounds to cooperate toward a shared goal, to communicate, to work together effectively, and to improve [88]. Each team member must be able to: (1) anticipate the needs of the others; (2) adjust to each other's actions and to the changing environment; (3) monitor each other's activities and distribute workload dynamically; and, (4) have a shared understanding of accepted processes and how events and actions should proceed [89].

Turning physician and nurse experts into an expert sedation team requires substantial planning and practice around explicit team-ness competencies [90]. There is a natural resistance to move beyond individual roles to a team mindset based on mutual accountability. Acceptance of the new required competencies is best achieved by a combination of clinically driven needs coupled with external educational and regulatory mandates; such as the American Academy of Pediatrics (*AAP*)/American Society of Anesthesiologists (*ASA*) Sedation Guidelines [91] and conducting a "time out" as set forth in the Universal Protocol to ensure fail-safe preoperative verification of the correct patient, procedure, site, and implants [92]. Adherence requires active discussion among all members of the surgical/procedure team, consistently initiated by a designated member of the team. The procedure is not started until any questions or concerns are resolved.

The importance of active discussions and teamwork has fostered an important initiative: the adoption of checklists. In 2009, a multi-institutional, international group of eight hospitals published prospectively collected data on a total of 7,688 consecutive patients, before and after the adoption of a Surgical Safety Checklist [93]. This was an initiative of the WHO Safe Surgery Saves Lives Program. This 19-item checklist was a concept long utilized by the aviation industry to improve safety. When applied in the medical context, the checklist improved team communication and consistent care. The mortality rate (at 30 days) decreased from 1.5 to 0.8% following implementation of the checklist with a decline in inpatient complications from 11 to 7% [93]. The airline industry, National Aeronautics and Space Administration (NASA), and federal aviation administration (FAA) have been developing checklists since before World War II [94–97]. As the surgical community has adopted lists to improve surgical safety and outcome [98], so too should the sedation community consider a global initiative at creating checklists to standardize care and improve patient outcome. One must also be aware that checklists can lead to automated behavior and reduced vigilance [99, 100]. Developing and implanting checklists that engender more systems awareness and clinician engagement are essential.

One can facilitate the "teamwork" processes by: (1) fostering a shared awareness of each member's tasks and role on the team through cross-training and other team training modalities; (2) training members in specific teamwork skills such as communication, situation awareness, leadership, follower-ship, resource allocation, and adaptability; (3) conducting team training in simulated scenarios with a focus on both team behaviors and technical skills; (4) training sedation team leaders in the necessary leadership competencies to build and maintain effective teams; and, (5) establishing and consistently utilizing reliable methods of team performance

evaluation. Future research on the role of teamwork and simulation training effectiveness in sedation needs to clearly address [88]:

- The training objectives: What Knowledge, Skills, Attitudes (KSA) are being trained?
- The design scenarios: How to directly link scenario events to training objectives. Ensure that the scenario includes events that trigger trainees to perform the specific competencies targeted for training using proven instructional design tools.
- The observer-based measures of teamwork process. This will allow researchers to assess whether teamwork KSAs improve with training.
- The training oriented to multidisciplinary teams so that medical team members are trained in the teamwork context in which they work.

Role of Risk Management and Patient Disclosure

When parents seek our medical care for their children, they entrust their child's welfare to us. Healthcare providers have a responsibility or "fiduciary duty" to act in the best interests of the patient [101]. Properly assessing the type of procedure planned (e.g., invasive vs. noninvasive); type and risk factors of the patient (e.g., ASA 1–4); type of drug to use (hypnotic vs. analgesic); type of team; and level of support is critical (see Table 22.6). When assessing the level of risk of the procedure, one should ask the following questions: What are the desired clinical effects? How quickly are effects desired? What is the desired duration of effects? Any adverse "other" clinical effects?

Table 22.6 Pediatric sedation risk factors

Airway obstruction history (snoring, stridor)
ASA risk stratification levels
Poor control of airway secretions
Craniofacial anomalies
Chronic lung disease
Myocardial dysfunction
Mental status changes
Poorly controlled seizures
Hydrocephalous, increased ICP
Acute illness – URI, cough, GI symptoms
GERD and bowel obstruction
Obesity

ICP intracranial pressure; *URI* upper respiratory tract infection; *GI* Gastrointestinal

"Qualified individuals" conducting sedations must possess education, training, and experience in: evaluating patients prior to moderate or deep sedation; rescuing patients who slip into a "deeper than desired" level of sedation or anesthesia; managing a compromised airway during a procedure; and, handling a compromised cardiovascular system during a procedure.

A growing driving force has been the push to encourage open and frank discussion with patients and their families after an occurrence of an adverse event with salutary effects [101]. Injured patients and their families want to know the cause of their child's bad outcomes, especially if the adverse event was caused by an error [102]. Studies show that the most important factor in people's decisions to file lawsuits is not negligence, but ineffective communication between parents and providers [102, 103]. Malpractice suits often result when an unexpected adverse outcome is met with no effort to apologize, with a lack of empathy from physicians and nurses, and a perceived or actual withholding of essential information [103, 104]. Studies consistently show that healthcare providers are understandably reticent about discussing errors, because they believe that they have no appropriate assurance of legal protection [105]. This reticence, in turn, impedes systemic and programmatic efforts to prevent medical errors [101]. The identified risks of non-disclosure after a perioperative event, are now changing organizational practices. Recent evidence from the University of Michigan supports the effectiveness of an aggressive disclosure policy [106]. In 2002, the University of Michigan Health System launched a program with three components: (1) acknowledge cases in which a patient was hurt because of medical error and compensate these patients quickly and fairly; (2) aggressively defend cases that the hospital considers to be without merit; and, (3) study all near misses and adverse events to determine how procedures and systems could be improved.

Disclosing an adverse event after pediatric sedation should occur when [107]: (1) a perceptible effect on the patient's well-being has occurred that was not discussed in advance as a known risk; (2) an event necessitates a change in the patient's care; (3) the event presents an important risk to the patient's future health, even if that risk is extremely small; and, (4) an anesthetic/surgical treatment or procedure has occurred without the patient's consent. From an ethical perspective, the disclosure process should begin at the time of discussing the consent for procedures and anesthesia interventions with the patients [108].

The Role of Best Practice Guidelines

Does application of the national guidelines decrease the risk of pediatric procedural sedation [109]? The American Academy of Pediatrics (AAP) and American Society of Anesthesia (ASA) Guidelines for sedation are expert opinion and consensus-based, and were developed in response to the growing number of pediatric sedations performed by nonanesthesiologists outside the operating room [91]. A prospective quality improvement evaluation of 960 coded sedation records (prospective data collection, retrospective analysis) showed a 4.2% complication rate with 3.8% related to mild to moderate sedation, and, 9.2% related to deep sedation [109]. A structured risk reduction program including (a) presedation risk assessment; (b) adherence to guidelines (e.g., monitoring); and, (c) avoidance of deep sedation improved sedation efficacy and safety.

Recent reports from the Pediatric Sedation Research Consortium on the incidence and nature of adverse events during pediatric sedation for procedures outside the operating room found that among 30,037 sedation encounters in 26 institutions, there was 1 ADE per 29 sedations, no deaths and two patients who had serious morbidity [110, 111]. The authors concluded that the most common adverse events are related to airway obstruction, apnea, secretions, and vomiting. The core deficient competencies identified were management of airway obstruction and respiratory depression. The single most important risk factor was proper patient risk assessment backed by "rescue" capabilities of the clinical microsystem when things went awry [112].

Summary: Looking Toward the Future of Pediatric Sedation

The healthcare system has only recently begun to approach patient safety in a more systematic way. There is a clear need to improve the quality of child sedation that presently permits an alarmingly high annual rate of medical errors that harm children and drive up costs. Effective sedation, controlling pain and anxiety, improves patient and parent satisfaction. Pediatric sedation is rapidly growing in its use around the world owing to its simplicity, cost savings, tolerance, and rapid emergence. The usual approach within medicine has been to stress the responsibility of the individual, and to encourage the belief that the way to eliminate adverse events is to get individual clinicians to perfect their practices. This simplistic approach to the safety of pediatric sedation is a disservice to both clinicians and their patients: It not only fails to address the important and complex systematic flaws that contribute to the genesis of adverse events in sedation, and perpetuates a myth of infallibility [112]. The focus on the actions of individuals, without addressing the underlying microsystem, as the sole cause of adverse events inevitably results in continued system failures and the resultant injuries and deaths of children.

Strategies to make sedation care more reliable and even safer might include: adoption of reliable engineering principles, setting up robust near miss reporting systems, applying critical event analysis tools, wide adoption of simulation and sedation team training, adopting checklists, standardizing medication protocols, implementing robust hand off protocols and patient identification checklists, and adherence to the AAP-ASA Sedation practice parameters. Attributing errors

to system failures does not absolve healthcare professionals of their duty to care. Rather, acknowledging system failures adds to that duty: the responsibility to admit and disclose errors, investigate them, and participate in redesign of the system.

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Part IV

Sedation into the Twenty-Second Century

Intravenous Infusions for Sedation: Rationale, State of the Art, and Future Trends

23

Anthony R. Absalom

Introduction

Benefits of the Intravenous Route of Administration

When sedation outside of the operating room is required, possible routes of administration of sedative agents include the inhalational, oral, intranasal, intramuscular, and intravenous routes.

Although administration of low doses of volatile anesthetic agents by inhalation can provide adequate sedation (and analgesia if nitrous oxide is also used), this mode of sedative administration is often not feasible outside the operating room. The bulky apparatus required to administer the agent, oxygen, and nitrous oxide, and to scavenge waste gases, is a significant limitation. Furthermore, distressed children are unlikely to cooperate sufficiently to tolerate a face mask or a "physiological" mouthpiece and the odor and taste of the agent throughout the period of administration.

With oral or enteral, transnasal, rectal, or intramuscular administration, the administered drug forms a depot that is absorbed slowly. Agents administered by the oral or enteral route are then subjected to significant first-pass metabolism. This problem is avoided with intramuscular injection, but this route is seldom used because it is painful. For all these routes, the rate at which drug reaches the systemic circulation is highly variable, since it also depends on factors such as gastric emptying, peristalsis, local pH, other contents of the gut, cardiac output, and mucosal or muscular blood flow. This results in considerable inter- and intra-individual variability in bioavailability when these routes are used. In patients who are in pain, distressed or unwell, absorption and systemic penetration of orally administered agents may be minimal. Thus, administration of standard doses of sedatives by these routes results in very variable blood concentrations and clinical effects, making it very difficult to judge in advance the required dose.

The problems of variable absorption and first-pass effects are avoided by intravenous administration as the entire administered dose reaches the systemic circulation. There remains considerable inter- and intra-individual variability in the relationship between administered dose and the blood concentration profile achieved (i.e., pharmacokinetics), but this variability is far less than with other routes of administration.

For any sedative agent, the blood and effect-site concentrations that will provide adequate sedation will depend on the sensitivity of the patient to the drug (pharmacodynamics), which can change with time and can be profoundly and unpredictably altered by coadministration of analgesics and other drugs. The required concentrations will also depend on the nature and

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severity of any noxious stimuli. Since the stimuli involved with any intervention change over time, as can the patient's susceptibility to the agent, so too will the effect-site concentration required for optimal sedation.

The inhalational route offers the ability to titrate the dose against the clinical effect, but suffers from the practical disadvantages discussed above. Of the remaining available routes of administration, only the intravenous route enables fine control of the blood concentration and clinical effects, particularly with newer agents that have "fast" kinetics, such as propofol. When administered as a single bolus, propofol has both a rapid onset and offset of action – the rapid onset is because the drug crosses the blood–brain barrier rapidly, and the rapid offset is because extensive redistribution to vascular tissues causes a rapid fall in blood concentrations and thus a decline in effect-site concentrations. With repeated boluses or an infusion, there is extensive redistribution of the drug into different tissues, but overall the drug does not "accumulate" significantly, in the sense that when administration ceases, blood concentrations fall fairly rapidly because hepatic metabolism is rapid compared with the rate of return of drug from the peripheral tissues.

If sedation with propofol is inadequate then blood and effect-site concentrations can be rapidly increased by the administration of one or more boluses, or an infusion. If on the other hand sedation is excessive, then cessation of further drug administration should result in a rapid decline in blood concentrations and clinical effect. The ability to make rapid and fine adjustments to the depth of sedation is probably the major advantage of intravenous administration.

With almost all intravenously administered anesthetic drugs, fixed rate infusions result in blood concentrations that increase significantly over time. One exception is remifentanil, which reaches steady-state blood concentrations after about 15 min of infusion at a fixed rate. The problem of increasing blood concentrations at constant infusion rates can be a trap for the unwary, since the relationship between infusion rate and clinical effect will change over time. A patient who is initially safe and adequately sedated may later become excessively sedated, with potentially life-threatening compromise of the airway and respiratory drive, despite there being no increase in the infusion rate. Steady-state blood concentration profiles are made possible by target-controlled infusion (TCI) systems, which facilitate titration of the blood concentration to the clinical effect, and will be discussed in detail later in this chapter.

Naturally, a disadvantage of intravenous administration is that intravenous access is required. Many children find this distressing, particularly if venous access is difficult because of obesity, or obliteration of the veins caused by prior administration of irritant drugs. The pain and discomfort of intravenous cannulation can be limited by prior application of a topical local anesthetic formulation, by distraction by a parent or play therapist, by the use of small gauge cannulae, and of course by rapid completion of the procedure by an experienced and skilled physician.

Choice of Agents

Pharmacokinetic and pharmacodynamic factors influence our choice of agents. Pharmacokinetics describes the relationship between drug dose and blood concentration, whereas pharmacodynamics is the study of the clinical effects themselves and of the relationship between blood concentration and clinical effect.

Ideally, a drug used for sedation should have a rapid onset of action and also a rapid offset of action. This requires an agent with a combination of favorable pharmacokinetic properties and pharmacodynamic properties, such as rapidly reached steady-state blood concentrations during infusion, a rapid rate of blood-effect-site equilibration, lack of accumulation, a rapid decline in blood concentrations on stopping the infusion (and ideally a context-insensitive half-time). By definition then, agents that are able to provide rapid, titratable, and controllable sedation must usually be administered by continuous infusion. Fentanyl is a good illustrative example. After a single dose, or a short duration infusion, fentanyl has rapid kinetics. Once repeated doses or an infusion lasting more than an hour have been given, the kinetics becomes slower and the context-sensitive half-time increases significantly,

making it unsuitable for use by infusion outside of the operating room or intensive care unit. Other intravenous agents that accumulate significantly and are not suitable for use by infusion or multiple bolus administration outside of the ICU are morphine, midazolam, and thiopentone.

Of the currently available drugs, those with suitable pharmacokinetics for use by infusion include ketamine, etomidate, propofol, and dexmedetomidine. Unfortunately, although ketamine has many suitable characteristics, such as maintained cardio-respiratory stability, bronchodilation, and potent analgesia, ketamine can cause problematic psychiatric phenomena. In sub-sedative doses in adults, it has been shown to cause several of the negative symptoms of schizophrenia [1, 2]. At sedative and anesthetic doses troublesome emergence phenomena are common, particularly when ketamine is used as the sole agent. These phenomena are less severe in children and can be attenuated by concomitant benzodiazepine administration. Etomidate commonly causes pain on injection and nausea and vomiting, and when used by infusion it is associated with significant adrenal suppression [3]. Indeed, in unwell adults, even single doses were shown to interfere with adrenal function for 24 h [4]. Another suitable agent is methohexitone, but unfortunately it is no longer widely available. Thus the only remaining agents which are suitable for use by infusion are propofol and dexmedetomidine.

Pharmacodynamics of Propofol and Dexmedetomidine

Propofol

The introduction of the intravenous hypnotic agent propofol into clinical practice has led to a significant increase in the popularity of the technique of total intravenous anesthesia (TIVA) in most of the world. TIVA is the exclusive use of the intravenous route for induction and maintenance of anesthesia. Strictly speaking, a technique involving intravenous infusions supplemented by nitrous oxide, for example, is not a TIVA technique. Exclusive use of the intravenous route for sedation is a natural extension of TIVA, since propofol and most other intravenous hypnotic agents produce anxiolysis and sedation at lower doses.

Part of the reason for the popularity of propofol is the favorable pharmacokinetic profile (see above, and later discussion), and the availability of infusion equipment to simplify and facilitate accurate and precise administration such as "calculator" infusion pumps and TCI systems. "Calculator" infusion pumps are simpler systems that can be programmed with the patient's weight so that the user can input a dose in mass-based units such as a bolus dose size in μg/kg or an infusion rate in μg/kg/min.

Another reason for the increase in popularity of TIVA is propofol's beneficial pharmacodynamic profile. At sub-sedative doses, propofol induces anxiolysis and amnesia [5, 6]. For procedures and environments that are frightening to children, these effects are highly desirable. In addition to anxiolysis, it produces a sense of well-being, and is associated with a very low incidence of nausea and vomiting [7, 8]. In fact, propofol has been shown to possess direct antiemetic properties at subhypnotic doses [9]. This is particularly beneficial in painful procedures requiring supplementary use of opioid analgesics that are likely to induce nausea and vomiting. With increasing doses, propofol produces dose-dependent sedation, with a gradual, step-wise decline in higher cognitive functions. For example, although functional imaging studies suggest that neurophysiological responses associated with processing of complex sentences is lost at very light levels of sedation [6], basic auditory perception of words continues for some time after loss of responses to command [10].

Propofol doses of course possess some undesirable pharmacodynamic effects. These include pain on initial intravenous injection, and dose-related cardio-respiratory depression. Pain on injection can be attenuated by many methods, and virtually eliminated by using a new propofol formulation containing medium chain triglycerides with added lidocaine [11]. The problems of respiratory and cardiovascular depression are dose-dependent, but can be somewhat unpredictable particularly in unwell patients. Propofol causes modest reductions in myocardial

contractility and more marked effects on systemic vascular resistance. At lower doses, there is a reduction in respiratory rate and tidal volume, obtunded airway reflexes, and obtunded responses to hypercarbia and hypoxemia. An anesthetic induction dose commonly causes a brief period of apnea. Moreover, when other agents are coadministered, marked synergism can occur, particularly with the opioids. Modest doses of propofol and remifentanil have been shown to increase the apnea threshold and markedly obtund the ventilatory response to hypercarbia [12]. These adverse cardio-respiratory effects of propofol are part of the reason why, in some quarters, it is felt that sedation with propofol should only be administered by anesthesiologists – for example the report of the Scottish Intercollegiate Guideline Network on procedural sedation in children recommends that propofol and other anesthetic agents should only be used by those "formally trained in paediatric or neonatal anaesthesia or intensive care" [13]. The ASA guidelines on safe sedation practices are not quite as proscriptive in the use of propofol by nonanesthesiologists, and rather only state that "practitioners administering propofol should be qualified to rescue patients from any level of sedation, including general anesthesia" [14].

Dexmedetomidine

Dexmedetomidine is an effective sedative agent, but produces a state of sedation which is unique among intravenous agents because the patient remains rousable even from relatively deep sedation. This difference is probably related to the fact that most other intravenous sedatives exert their clinical effects via a different mechanism (an agonist effect on $GABA_A$ receptors on inhibitory neurons in the thalamus and other areas), whereas dexmedetomidine appears to exert its clinical effects by acting as a highly selective *a*2 adrenergic agonist (i.e., having minimal effects on the *a*1 receptor sub-type), which results in enhanced activity in a NREM sleep-promoting pathway [15]. An agonist effect on *a*2 receptors results in inhibition of the locus coerelus, which is thought to disinhibit the ventrolateral preoptic (VLPO) nucleus, causing increased GABA release from VLPO neurons resulting in decreased activity in the tubo-mammillary nucleus (TMN). Natural NREM sleep is also associated with increased firing of VLPO neurons. Since the TBM is the only neuronal source of histamine, which causes arousal, this action on the TBM results in reduced histamine release and sleep or sedation.

In addition to the benefit of rousability, the promotion of natural sleep may bring other benefits such as the restorative functions of sleep. Disturbances of natural sleep are known to cause cognitive and mood changes, and to have adverse effects on immunity. In addition, recent work suggests that dexmedetomidine may modulate the inflammatory response in critically ill patients and in septic animals [16, 17].

Finally, the *a*2 adrenergic receptor agonists have several other beneficial effects. These include analgesia and an opioid sparing effect when used during painful procedures, and slowing of the heart rate and protection against myocardial ischemia (shown in adults). In high doses it can cause vasoconstriction, but in lower doses it causes mild vasodilation and only minor effects on the blood pressure. Respiratory drive is reasonably well maintained.

These pharmacodynamic benefits, coupled with a pharmacokinetic profile that makes it suitable for use by infusion, have led to increased use of dexmedetomidine for sedation. When used as the sole agent for sedation for computed tomography and magnetic resonance imaging studies, dexmedetomidine has been shown to produce reliable and effective sedation with acceptable hemodynamic stability and no adverse effects on respiratory parameters [18–21].

Basic Principles of Pharmacokinetics

What Is a Pharmacokinetic Model and How Is it Derived?

A pharmacokinetic model is a mathematical model that can be used to predict the blood concentration profile of a drug after a bolus

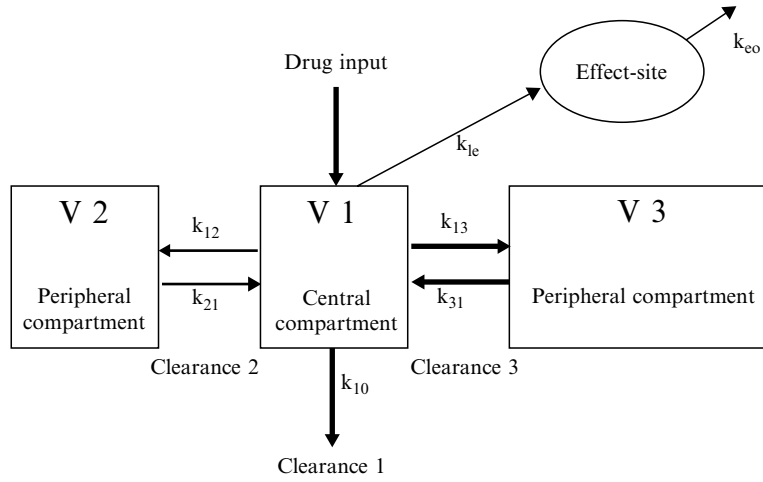

Fig. 23.1 The three compartment pharmacokinetic model enlarged with an effect compartment. (Reprinted with permission from Absalom and Struys [77])

dose or an infusion of varying duration. Some types of models, such as recirculatory models, approximate human physiology by estimating blood volume, cardiac output, and blood flow to different organs or groups of organs [22–26].

The most commonly used models are the so-called mammillary, compartmental models, as illustrated in Fig. 23.1. In order to understand these models, some understanding of the mathematics of exponential processes is necessary (see below). It is important to remember that compartmental models are purely mathematical models. They are typically derived by measuring the arterial or venous plasma concentration of a drug after a bolus or infusion in a group of patients or volunteers, and then estimating the pharmacokinetic parameters of the drug under investigation by performing nonlinear mixed effects modeling with software such as NONMEM® (Globomax LLC, Hanover, USA). During this process, the investigators typically begin with a simple model, and then make stepwise increases in the complexity of the model. Increases in complexity that do not significantly improve the ability of the model to predict measured blood concentrations are rejected in favor of the simpler model.

Important Mathematical Concepts for Understanding of Pharmacokinetic Models

Many physiological processes depend on concentration gradients and so display first-order kinetics (Fig. 23.1). For most anesthetic agents, the enzymes involved in metabolism are not saturable at clinical concentrations, and thus the amount of drug metabolized during any unit of time depends on the plasma drug concentration at that time. Similarly, for the anesthetic agents, redistribution is a passive process in which the rate and direction of redistribution depend on the concentration gradient between the blood and other tissues.

For any first-order process, the variable of interest changes in an exponential manner. Depending on the process, the variable may either increase or decrease exponentially. When the variable of interest is an amount (e.g., the mass of drug or the number of millimoles of drug) then the changes in this variable over time can be described mathematically in the following general way (the formula applies equally well to other exponential process such as population growth, or the arterial blood pressure changes during diastole):

$$A(t) = A(0) \times e^{k \times t},$$

where $A(0)$ is the amount at time zero, t is the time since the start of the process, $A(t)$ is the amount at time t, k is the rate constant (with units of the inverse of time – typically min^{-1}), and e is an irrational constant approximately equal to 2.7182. The rate constant k describes the proportional change over a unit of time. If $k=1$, then $A(t)$ increases by a multiple of e^1 in each unit of time – i.e., $A(t)$ increases by 271.8% in each unit of time. On the other hand if $k=-1$, then $A(t)$ changes by a factor of e^{-1} $(=1/e=0.367)$ in each unit of time which means that $A(t)$ decreases by 63.3% in each unit of time.

The rate of change of $A(t)$ at time t can be calculated mathematically as the first differential of $A(t)$ as follows:

$$dA(t)/dt = k \times A(0) \times e^{k \times t} = k \times A(t).$$

Thus although the proportional change is constant, the absolute change over a unit of time changes according to the amount, $A(t)$, present during that unit of time.

In pharmacology, we are often more interested in concentrations than amounts, and we are commonly dealing with situations where gradients decline over time. For these situations, the following general equation will apply:

$$C(t) = C(0)e^{-k \times t},$$

where $C(0)$ is the concentration at time zero, t is the time since the start of the process (e.g., the time since drug administration), $C(t)$ is the concentration at time t, and k is the rate constant.

Half-Life, Time Constant, and Rate Constant

The time constant, t, is another rate descriptor, but it is described in units of time. Mathematically, it is calculated as the inverse of the rate constant (i.e., $1/k$), and represents the time taken for a change by a factor of e (i.e., an increase of 271% or a decrease of 63%).

Rate and time constants are not always intuitively easy to understand, and thus the pharmacology literature often uses half-lives to describe the time course of exponential processes. Simply put, the half-life describes the time it takes for a change by a factor of 2 – i.e., for the amount to change to double or half the initial value. By definition the half-life is shorter than the time constant. Mathematically, the half-life can be calculated as follows:

$$t1/2 = \tau \times \ln 2 = \tau \times 0.693 = 1/k \times 0.693.$$

Volume of Distribution

If serial measurements of the concentration of a drug can be performed, then it is possible, with knowledge of the time course of drug administration, and appropriate mathematical techniques, to calculate a volume of distribution (an apparent volume in which the drug has been distributed). Few drugs distribute uniformly throughout the body. Most distribute into different tissues at different rates. In these situations, an "initial volume of distribution" (V_1 or V_c) is often described. It can be calculated as follows:

$$V_d = \text{Dose} / C(0).$$

Since drugs do not mix instantaneously on injection, $C(0)$ is calculated by extrapolating the time-concentration curve back to time zero. If the volume of distribution, V_d, is ~5 L then it is likely that the drug has initially mixed within the circulating blood volume, whereas a drug with a V_d closer to ~12 L is likely to have initially mixed within the extracellular fluid.

The volume of distribution at steady state, V_{dss}, is the apparent volume of distribution once adequate time has been allowed for complete equilibration of the drug across all tissues. In multi-compartmental models, V_{dss} is the mathematical sum of the volumes of all compartments in the model. For drugs with extensive protein binding and/or high lipid solubility, the peripheral tissues will have a large capacity to absorb the drug resulting in a V_{dss} greater than the volume of the entire body.

Single Compartment Pharmacokinetic Models

The behavior of a drug that does not undergo redistribution can be described by a single-compartment mathematical model. On injection, the drug distributes uniformly throughout a single volume, and thus the volume of distribution, V_d, is equal to the volume of the single compartment, V, and the drug concentration in this compartment is the same as the plasma concentration. After a single bolus or an infusion, the drug concentration will fall because of metabolism or elimination, as described by the following equation:

$$C_p(t) = C_p(0) \times e^{-k_{el} \times t},$$

where $C_p(t)$ is the plasma concentration at time t, $C_p(0)$ is the initial plasma concentration, and k_{el} is the elimination rate constant, and $t=0$ is the time of the bolus or the time at which the infusion ceased. Clearance (mL/h) can be calculated from k_{el} as follows:

$$\text{Clearance, Cl} = k_{el} \times V_d.$$

If the relationship between drug concentration and time is plotted on linear axes, then the exponential decline results in a curved graph (Fig. 23.2). If, however, a semi-logarithmic graph is used (i.e., the logarithm of the concentration is plotted) a straight line will result. Figure 23.3 shows the relationship between $\text{Log}_e\ C_p(t)$ and time.

As shown, the elimination rate constant can be calculated from the slope of the line in Fig. 23.3. If the natural logarithm ($\log_e$, generally abbreviated to "ln") of the drug concentration is plotted against time, then the slope is simply equal to k_{el}. As there is only one rate constant influencing the rate of decline in drug concentration, the decline in plasma concentrations has a constant $t_{1/2}$ that can be calculated from k_{el} as shown above.

Three-Compartment Models

The pharmacokinetics of most anesthetic drugs can be described with reasonable accuracy by a three-compartment model. Each model describes the number of compartments, and their volumes, the rate of drug metabolism or elimination, and the rate of transfer of drug between the different compartments. The concept is summarized in Fig. 23.1.

By convention, the compartment into which the drug is injected is called the central compartment (V_1 or V_c). This compartment may thus be thought of as including the blood volume, although it is often far larger than the blood volume. It is sometimes referred to as the initial volume of distribution. Elimination of active drug by metabolism usually occurs from within this

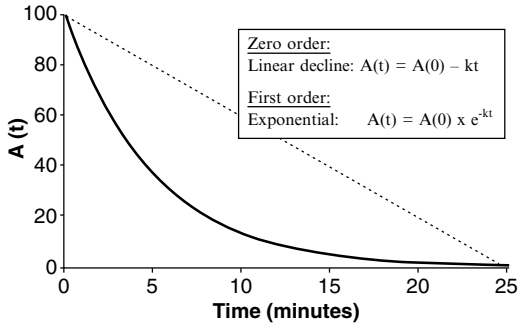

Fig. 23.2 Exponential versus linear decay – the (*dotted*) *straight line* represents linear decay, in which the amount of drug at time t is a linear function of the initial amount. The curve (*solid*) illustrates exponential decay in which the amount of drug at time t is an exponential function of the initial amount

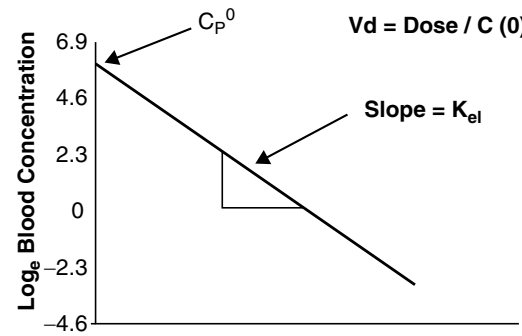

Fig. 23.3 The relationship between $\log_e$ drug concentration and time after a bolus of a drug with single compartment kinetics. The slope of the elimination curve is constant

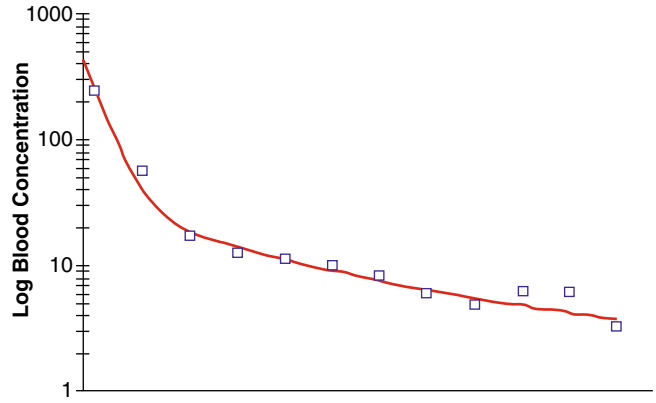

Fig. 23.4 Relationship between plasma concentration (after a bolus dose) and time for a typical anesthetic agent, displaying tricompartment kinetics. The *squares* represent typical measured concentrations and the *red line* represents a curve generated the sum of three exponentials

compartment (as in the case of hepatic or renal metabolism). The rate of elimination is described interchangeably by a rate constant (k_{10}), or a clearance (clearance $= k_{10} \times V_1$). The second compartment, V_2, is referred to as the "rapid re-distribution" compartment since drug concentrations in V_2 equilibrate rapidly with those in the central compartment. The rate constants k_{12} and k_{21} are used to describe the rate of drug transfer from V_1 to V_2 and from V_2 to V_1, respectively. Fast redistribution clearance "Clearance 2" can be calculated as:

$$\text{Clearance 2} = k_{12} \times V_1 = k_{21} \times V_2.$$

The third compartment, V_3, is often referred to as the "slow" compartment (because there is rather slower drug distribution between V_1 and V_3). Here the rate constants k_{13} and k_{31} are used to describe the rate of drug transfer from V_1 to V_3 and from V_3 to V_1, respectively. Slow redistribution clearance "Clearance 3" can be calculated as:

$$\text{Clearance 2} = k_{12} \times V_1 = k_{21} \times V_2.$$

The second and third compartments are sometimes referred to as the "vessel-rich" and "vessel poor" compartments respectively, but these terms are best avoided since they encourage the false impression that these compartments represent distinct anatomical or physiological entities. The sum of V_1, V_2, and V_3 gives the "volume of distribution at steady state," V_{dss}.

Naturally the site of action of the anesthetic agents is not in the vascular system, but in the brain at a vaguely defined "effect-site." Thus many models now also include the effect-site as a fourth compartment, with the rate constant k_{eo} being used to describe the rate of equilibration between the central and effect-site compartments.

For a drug showing three-compartment kinetics (such as propofol), the change in concentrations after a bolus or infusion cannot be described by a single rate constant or half-life. Because the plasma concentration is influenced by several simultaneous exponential processes, the decline in concentration is more complex to describe, since the time required for the concentration to fall by 50% (or any other proportion) changes over time. Figure 23.4 shows a typical curve of the relationship between blood concentration and time after a single bolus dose of an anesthetic drug. The time course of changes in plasma concentration shown in Fig. 23.4 can be described mathematically as the sum of three exponential processes:

$$C_P(t) = A \times e^{-\alpha t} + B \times e^{-\beta t} + C \times e^{-\gamma t},$$

where A, B, C, a, b, and g are constants. As can be seen in Fig. 23.4, in the early phase after a bolus dose, the plasma concentration falls rapidly, being mostly influenced by rapid redistribution (described by a rate constant a). Later on the rate of decline in plasma concentrations is influenced mostly by redistribution to less well-perfused

tissues (described by a rate constant *b*). Eventually the predominant factor is elimination (rate constant *g*). From these parameters, the time-honored redistribution and elimination half-lives can be calculated.

During and after administration of repeated bolus doses or infusions, the changes in drug concentrations vary in a complex matter since they are influenced by several simultaneous exponential processes, and the relative contributions of the different processes change for most anesthetic drugs as the duration of infusion increases. These factors make it difficult to predict drug concentrations without the assistance of computer programs.

Context-Sensitive Half-Time

The concept of "context-sensitive half-time" (CSHT) has been introduced as a simple metric that provides a summary of the interplay of time and the different half-lives after an infusion [27]. It describes the time taken for blood concentration of a drug to fall by 50% after the end of an infusion of a specified duration – the context is thus the duration of infusion. The influence of duration of infusion on context-sensitive half-time indicates the degree of drug accumulation, and the balance between redistribution and metabolism/elimination. This metric only describes the time taken for the first decline of 50% – the time taken for subsequent 50% falls will be different. Also, it does not necessarily describe when clinical effects will cease, since these depend on the initial concentration, and pharmacodynamic factors such as the sensitivity of the patient to the drug. Nonetheless, it gives the physician a useful indicator of the rate at which drug concentrations will decline after an infusion, and an indication of the influence of duration of infusion.

Pharmacokinetic Models for Propofol

Tables 23.1 and 23.2 show the model parameters for the published pediatric propofol pharmacokinetic models.

Table 23.1 Comparison of model parameters for the Schuttler, Short and Marsh pediatric models for propofol

	Schüttler (20 kg, 5 years)	Short	Marsh (pediatric)
V_1	0.384 L/kg	0.432 L/kg	0.343 L/kg
K_{10} (min^{-1})	0.073	0.0967	0.1
K_{12} (min^{-1})	0.135	0.1431	0.0855
K_{13} (min^{-1})	0.06	0.0392	0.021
K_{21} (min^{-1})	0.05	0.1092	0.033
K_{31} (min^{-1})	0.00174	0.0049	0.0033

During the early 1990, Marsh and colleagues studied the accuracy of TCIs using an adult propofol model in 20 children, and found it to be associated with a significant overestimation in the blood concentrations (i.e., measured blood concentrations were less than expected) [28]. This was consistent with the findings of several groups of workers who have found that the pharmacokinetics of propofol differs between children and adults [29, 30]. The Marsh adult model was then revised to produce a model specific to children (the size of the central compartment volume was increased, but remained a linear function of body weight), and when prospectively tested, the predictive performance was better than when the adult model was used [28]. Since then several other models specific to children have been produced.

Schüttler published a complex model in 2000, based on a combined analysis of data from several other studies [31]. This model, which contains multiple covariates, and adjusts for mode of drug administration (bolus vs. infusion) and sampling site (arterial vs. venous), was designed for use in a wide range of patients including children. The Short model, on the other hand, was designed specifically for the pediatric population [32], but like the Schüttler model it is seldom used in clinical practice. The parameters of these models are summarized in Table 23.1.

Two models are commonly used at present – the Kataria and Paedfusor models (Table 23.2). Despite the fact that they were developed in different ways, and that weight is incorporated in a different way in each model, the overall model parameters are fairly similar. Figure 23.5 shows a comparison of the cumulative propofol dose for

Table 23.2 Kataria and Paedfusor pediatric propofol models

	Paedfusor [34, 78]		Kataria [33] Weight proportional		Kataria Weight proportional, age adjusted	
	Model	20-kg patient	Model	20-kg patient	Model	5 years, 20-kg patient
V_1	0.458 L/kg	9.2 L	0.52 L/kg	10.4 L	0.41 L/kg	8.2 L
V_2	1.34 L/kg	26.8 L	1.0 L/kg	20 L	0.78 L/kg + (3.1 × age) − 16	15.1 L
V_3	8.20 L/kg	163.9 L	8.2 L/kg	164 L	6.9 L/kg	138 L
K_{10} (min^{-1})	$70 \times Weight^{-0.3}/458.4$	0.062	0.066	0.066	0.0854	0.0854
K_{12} (min^{-1})	0.12	0.12	0.113	0.113	0.1878	0.1878
K_{13} (min^{-1})	0.034	0.034	0.051	0.051	0.0634	0.0634
K_{21} (min^{-1})	0.041	0.041	0.059	0.059	$0.077 \times weight/V_2$	0.1020
K_{31} (min^{-1})	0.0019	0.0019	0.0032	0.0032	0.0038	0.0038

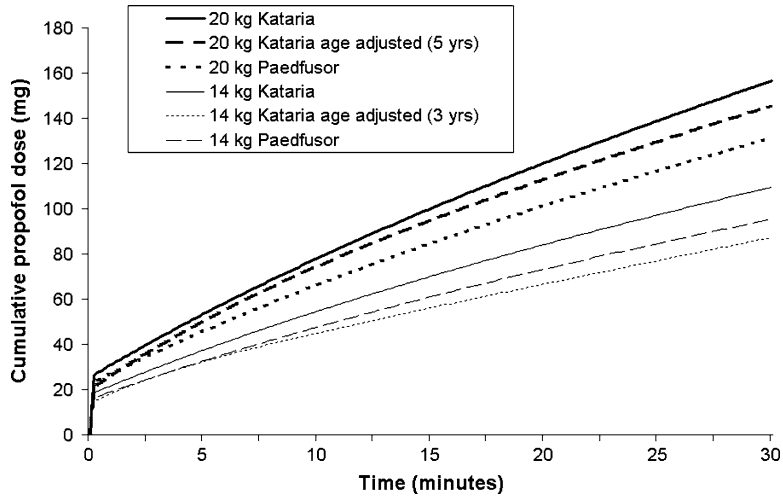

Fig. 23.5 Cumulative propofol doses administered to children weighing either 12 or 20 kg, by TCI systems programmed with the Kataria or Paedfusor pharmacokinetic models for propofol (target concentration 2.5 μg/mL)

children weighing 14 and 20 kg, when the Kataria and Paedfusor models are used to administer a target blood concentration of 2.5 μg/mL.

Kataria et al. used three different pharmacokinetic modeling techniques in an extended group of children between 3 and 11 years, and found that the pharmacokinetics of propofol could be described by a three-compartment model [33]. They found that a weight-proportional model performed significantly better than a model with fixed volumes and rate constants. Adjusting V_2 (and hence k_{12} and k_{21}) according to age produced a further (modest) improvement. Although Kataria recommended that the weight-proportional model be used, some investigators have used the weight-proportional model with age adjustment. The equation used to adjust V_2 for age is likely to yield an anomalous (negative) V_2 for children younger than 3 years, and thus the age-adjusted, weight-proportional model should not be used in children younger than 3 years.

The Paedfusor model [34] was adapted from one of the preliminary models developed by Schüttler prior to the publication of his final model [31], and was incorporated in a pediatric TCI pump developed and used in Glasgow. In the Paedfusor model, the central compartment volume and clearance have a nonlinear correlation with weight, whereas in the final Schüttler model all variables have a nonlinear correlation with age and weight.

Pediatric Propofol Infusion Regimens

Disadvantages of Repeated Bolus Dose Administration

Although it is possible to maintain sedation or anesthesia with repeated boluses of an intravenous sedative agent, this is far from ideal. First, stable levels of sedation are not possible since the blood and effect-site concentrations will be constantly either rising or falling. If the bolus size is too big, the patient state will oscillate from excessive sedation/anesthesia, with the attendant risks, to inadequate sedation. Second, it is difficult to judge the dose required to produce adequate, but not excessive blood concentrations. Finally, it is also difficult to judge the required interval between doses. Figure 23.6 shows the estimated blood concentrations arising from repeated 40 mg boluses of propofol administered to a 20-kg child. In these simulations, a bolus was administered each time the estimated concentration fell to 2 μg/mL. As can be seen, as drug accumulates in peripheral tissues, the rate of decline in blood concentration after successive doses gradually decreases, resulting in an increase in the interval between doses.

Commonly Used Regimens

Typically, blood concentrations of the order of 2–3 μg/mL are required for sedation in children. Naturally the concentration required is influenced by multiple other factors such as coadministered drugs. Thus, it is not surprising that after cardiac surgery, Murray et al. found that the mean measured propofol concentration at recovery of consciousness was only 0.97 μg/mL; whereas Rigouzzo et al. found that the EC50 (of measured blood propofol concentration at steady state) associated with loss of consciousness in healthy children was 4.0 μg/mL [35].

In Cambridge a commonly used deep sedation regimen is an initial bolus of 2 mg/kg followed by an infusion at 10 mg/kg/h (in children <1 year of age, higher doses may be required, e.g., an initial bolus of 3 mg/kg and higher initial infusion rates). Figure 23.7 shows a simulation of the regimen, with the concentrations estimated by the Paedfusor model. At about 10 min after the initial bolus, the blood concentrations reach a nadir of ~2.5 μg/mL. If the infusion rate is kept constant at 10 mg/kg/h, the blood and effect-site concentrations, and clinical effect will gradually increase (reaching ~5 μg/mL after several hours), which is why downward titration of the infusion rate is commonly required.

In a recent study, Koroglu and colleagues administered a 3 mg/kg bolus followed by

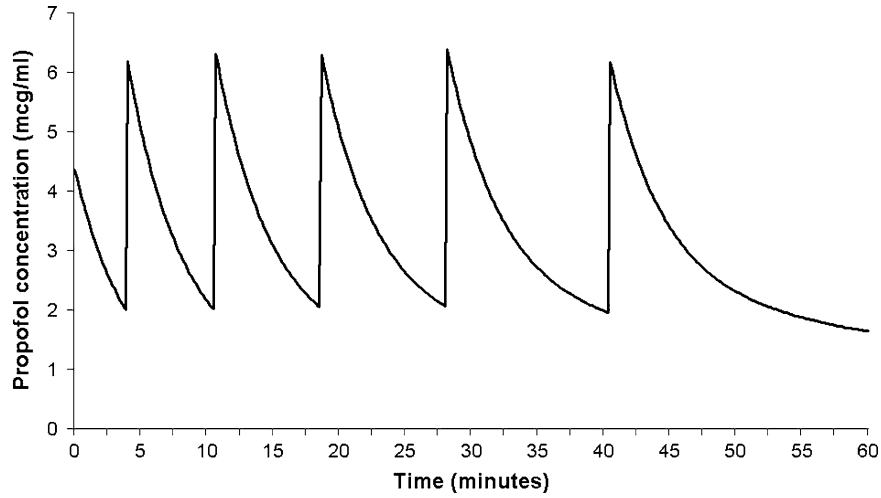

Fig. 23.6 Estimated blood propofol concentrations resulting from repeated 40 mg boluses of propofol in a 20-kg child. In this simulation, a repeat bolus was administered each time the estimated concentration fell to 2 μg/mL. Note how the rate of decline in concentration after successive doses gradually decreases; resulting in an increase in the interval between doses

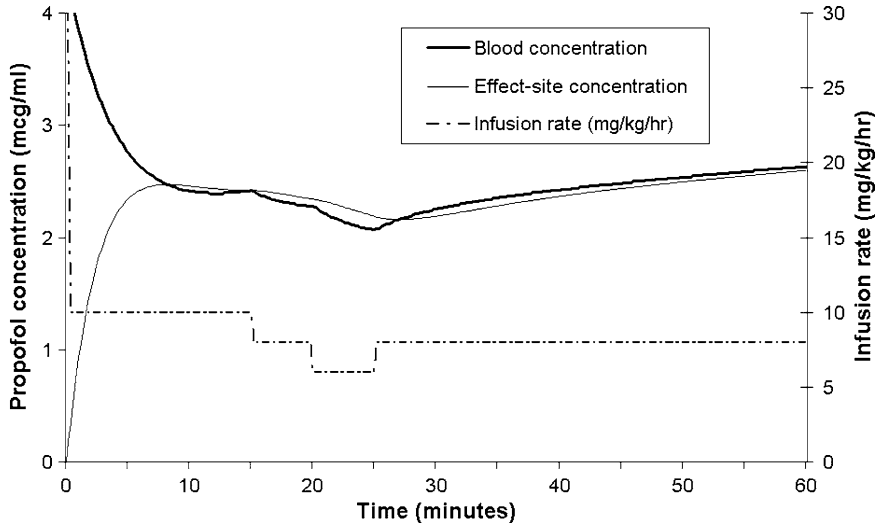

Fig. 23.7 Blood and effect-site concentrations (*heavy* and *light continuous lines* respectively, as estimated by the Paedfusor model with a k_{eo} of 0.91 min^{-1}), arising from an initial bolus of 2 mg/kg, followed by an infusion initially at 10 mg/kg/h. Note the slow blood and effect-site concentration changes after step changes in infusion rate at 15, 20, and 25 min. Also, note that the concentrations continue to rise when the infusion rate is kept constant

infusions of 100–15 μg/kg/min (i.e., 6–9 mg/kg/h) of propofol to 30 children between 1 and 7 years of age for sedation during MRI scans [18]. With this propofol regimen, sedation was adequate in 27 of the 30 children, cardio-respiratory stability were reasonable, and mean recovery and discharge times were 18 and 27 min, respectively.

PK Models for Dexmedetomidine

Pharmacokinetic models for dexmedetomidine in children have recently been produced from studies involving single bolus administration [36], after short infusions [37], and after longer infusions [38] for postoperative sedation. Further studies are needed to compare the predictive accuracy of these models to determine which perform optimally in clinically relevant situations.

Infusion Regimens for Dexmedetomidine

Typical infusion regimens comprise an initial bolus over 10 min, followed by a continuous infusion. Mason used an initial bolus of 2 μg/kg over 10 min (repeated if Ramsay sedation score [39] of 4 not reached) followed by an infusion at 1 μg/kg/min, in 62 patients with mean age 2.8 years and mean weight 15 kg, undergoing CT imaging [19]. Of these patients, 10% were able to undergo their scan during the initial loading dose, 16% required a second loading dose, and 90% required the maintenance infusion. Two patients became agitated during the loading dose, and were given alternative agents for sedation. Subsequently, Mason et al. reported the results of a study of the use of higher doses of dexmedetomidine in >700 patients undergoing MRI scanning, which is more stimulating, and in which movement causes significant image degradation [21]. With time their regimen evolved from an initial bolus of 2–3 μg/kg, and from an initial infusion rate of 1–1.5 and 2 μg/kg/h. The highest doses were associated with successful sedation and image acquisition in 97.6% of patients, but with reasonable cardio-respiratory safety.

Koroglu and colleagues used smaller doses for sedation during MRI scanning in 30 children with a mean age of 4 and mean weight of 14 kg – the bolus dose was 1.0 μg/kg over 10 min, and this was followed by an infusion at 0.5 μg/kg/h initially, but increased to 0.7 μg/kg/h if a Ramsay

score of 5 was not reached within 25 min [18]. With this regimen, additional midazolam was required in 16% of patients to facilitate successful scan completion.

Target Controlled Infusions

Definition

A target controlled infusion (TCI) is an infusion of a drug administered by an infusion pump controlled by a computer or microprocessor that is programmed to calculate and implement the drug infusion rates required to achieve in a patient the blood or effect-site concentrations required by the user. Simply put, with these systems, the user inputs a desired, "target" concentration, and the system uses the parameters of a pharmacokinetic model for that drug and the patient parameters included as covariates in the pharmacokinetic model, to calculate the infusion rates estimated to be necessary to achieve that concentration.

Rationale for TCI

As explained above, bolus doses of intravenous drugs for sedation are generally only suitable for short procedures. Although infusions do provide more stable conditions, they still do not provide stable blood concentrations – even for propofol, a drug with rapid kinetics, blood concentrations continue to rise for several hours when fixed rate infusions are used (see Fig. 23.7). There is thus a poor correlation between infusion rate and clinical effect. During the course of any procedure, the effect-site concentration required for adequate sedation will vary widely according to several other factors such as the influence of coadministered drugs (especially opioid analgesics), the onset of natural sleep, changes in the environment, and the severity of any noxious stimuli. The changing relationship between infusion rate and effect-site concentration, and the delay in blood-effect-site concentration equilibration, makes rational, precise, and rapid titration of the infusion very difficult. As can be seen in Fig. 23.7, step-wise changes in the infusion rate of 2 mg/kg/h result in very slow change in blood and effect-site concentrations, so that it is difficult to assess the response to an infusion rate adjustment. These difficulties form an important part of the rationale for TCIs, where a computer or microprocessor is used to implement the infusion rates required to maintain steady-state blood concentrations. Since steady-state blood concentrations arise quite quickly, TCI systems allow the user to judge the clinical effect of a blood concentration and then to adjust the target blood concentration accordingly, rather than adjusting the infusion rate accordingly. An analogy is to compare the control a car driver has over the speed of his car, when he has a speedometer and cruise control system, versus the control he would have with only a gas pedal and no cruise control system or speedometer.

When k_{eo} values for children have been validated and effect-site targeting is sufficiently developed for use in children, then a further refinement will be added since users will then be able to titrate the effect-site concentration according to observed patient responses.

With blood and effect-site concentration targeting, absolute accuracy of the pharmacokinetic model is not important, since steady-state concentrations arise very quickly, and there remains wide variability in pharmacodynamic sensitivity among different patients to given blood and effect-site concentrations. Thus, even with the most accurate models and systems, titration according to pharmacodynamic responses will be required.

Principles of TCI

With a TCI the user is able to set and alter a desired "target" drug concentration. The target is usually a blood concentration (although algorithms do exist for effect-site targeting [40] and have been implemented for propofol, remifentanil, and sufentanil use in adults). TCI systems use compartmental pharmacokinetic models with complex mathematical algorithms to calculate and implement the infusion rates required to

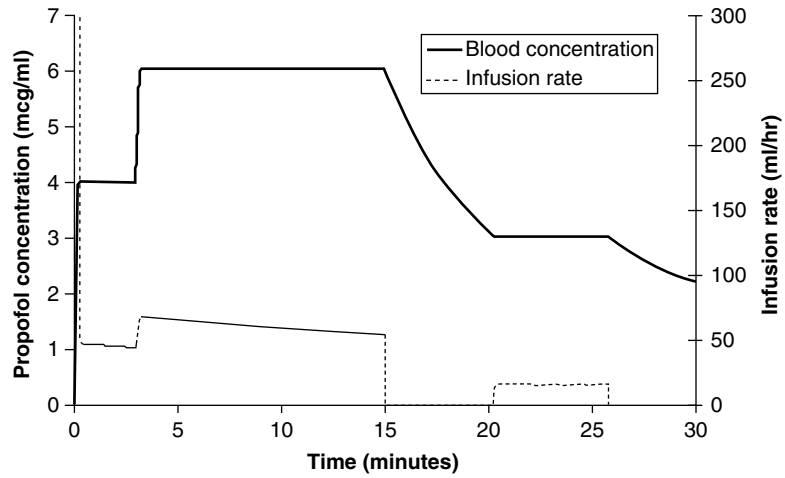

Fig. 23.8 Blood concentration targeted TCI, showing the infusion rates required by the Paedfusor model for a child weighing 20 kg. At time zero the target is set at 4 μ/mL, at 3 min it is increased to 6 μg/mL, and at 15 min the target is reduced to 3 μg/mL

achieve the target concentration. Every 10 s the system software calculates the drug amount in each of the compartments, taking into account the amount of drug infused over the previous 10 s, the movement of drug into and out of the central compartment by redistribution, and the rate of removal of active drug from the central compartment by metabolism or elimination. It then calculates and implements the infusion rate required to maintain the target concentration over the subsequent 10 s.

The theoretical foundations for a system designed to maintain and achieve a steady-state blood concentrations were laid by Kruger-Thiemer in 1968 [41], and later developed and refined by Vaughan and Tucker [42, 43], and Schwilden [44] (who developed the first clinical application of this theory – the "computer-assisted total intravenous anaesthesia system"). The schemes developed by these pioneers for drugs conforming to two-compartment models became known as BET (bolus, elimination, transfer) schemes, so-called because they comprised an initial bolus to fill the central compartment (size in mg = target concentration × V_1), followed by two superimposed infusions, one to replace drug lost by elimination and the other to replace drug lost by redistribution. Modern TCI systems continue to use methods based on this approach, except that most modern models comprise three compartments. After the initial bolus, three superimposed infusions are computed. When the target concentration is constant, drug lost by elimination is replaced by a constant rate infusion, since a fixed proportion of the total amount of drug in the central compartment is eliminated in each unit of time. By contrast, the amount of drug distributed to peripheral tissues declines exponentially as the gradient between the central compartment and the peripheral compartments decreases. Thus two infusions at exponentially declining rates are required to replace drug "lost" from the central compartment by fast and slow redistribution. The sum of these three infusions is naturally an infusion at a decreasing rate.

When the user decreases the target concentration, the infusion systems stop infusing drug, until it calculates that the blood concentration has decreased to the target concentration, whereupon the infusion restarts (see Fig. 23.8).

The first commercially available TCI systems contained the Diprifusor®, a microprocessor that was embedded in intravenous infusion pumps sold by several manufacturers from 1996 onward (in numerous countries around the world, but not in the USA). The development of the Diprifusor® has been described in detail [45, 46]. TCI pumps controlled by it can only administer TCIs of propofol, and only if the microprocessor is able to detect the presence of single-use prefilled glass syringes of 1 or 2% propofol purchased from AstraZeneca. These syringes contain a programmable metallic strip in the flange that is detected by a sophisticated process called programmed

magnetic resonance. When the syringe is almost empty, the strip is "de-programmed" so that it cannot be reused.

In the years since the release of the first generation of TCI systems, the patent for propofol has expired. While the cost of the prefilled syringes from AstraZeneca has changed very little, significantly cheaper generic forms of propofol are now available. Until recently, propofol purchased from other manufacturers could not be used in TCI propofol systems, but this has now changed with the development and launch of second generation of TCI system, the so-called "Open TCI" systems. These systems allow the use of a variety of drugs, administered from a variety of syringes and sizes. Thus, when used to administer generic propofol formulations, these pumps can generate cost savings of up to 80% of the cost of the original propofol formulation. Two currently available systems are the Alaris Asena PK® (Alaris Medical Systems, Basingstoke, UK) and the Base Primea (Fresenius, Brezins, France).

Choice of Propofol Target Concentration

In general, blood concentrations between 2 and 3 μg/mL are required for sedation in children. However, there are no hard and fast rules, and it is important to remember that use of a TCI system does not remove the requirement for titration of the target concentration according to the clinical response, since there is very broad intra- and inter-individual pharmacodynamic variability. Unfortunately, there is very little data at present on the target concentrations required during sedation. There have been some studies of the concentrations required for loss of consciousness and so, for safe sedation, it is worth bearing these in mind. Hammer and colleagues investigated the TCI propofol requirements for preventing a movement or hemodynamic response to oesophagogastroduodenoscopy in 12 children between 3 and 11 years of age [47]. The EC50 (i.e., the propofol concentration estimated by the age-adjusted Kataria model at which 50% of patients did not respond) in this group was 3.55 μg/mL when calculated using Dixon's up–down method [47] and 3.7 μg/mL when recalculated using logistic regression [48]. In 45 children between 6 and 13 years of age, Rigouzzo et al. found that the mean target propofol concentration (Kataria age-adjusted model) associated with a BIS (bispectral index) of 50 (i.e., surgical anesthesia) was 3.0 μg/mL, and the mean measured propofol concentration associated with BIS 50 was 4.3 μg/mL [35].

Predictive Performance of PK Models During TCI

Most studies of the validity and accuracy of models used for TCI have used the parameters recommended by Varvel for assessing the predictive performance of a model during TCI – bias, imprecision, wobble, and divergence [49]. Generally, bias <20% and imprecision <40% are considered acceptable [50, 51].

Although not yet common in clinical practice, there is a growing body of experience of TCI administration of propofol in children. Some studies have studied predictive performance of TCI systems during anesthesia in children. Absalom and colleagues assessed the predictive performance of the Paedfusor model in 29 children aged between 1 and 15 years who were undergoing cardiac surgery or cardiac catheterization [34]. Predictive performance was well within the acceptable range. Bias was 4.1% indicating that on average the measured blood concentrations were 4% higher than predicted; while the imprecision was 9.7%, indicating that 50% of measured blood concentration samples were in the range from 90.3 to 109.7% of the target concentration [34].

Engelhardt and colleagues used a simple manual infusion regimen designed to manually target three different propofol concentrations in children, and then assessed the ability of the Kataria model to predict the measured concentrations [52]. In this study, the bias was 6.98% and the imprecision 17.3%. Rigouzzo and colleagues used the age-adjusted Kataria model for TCI

administration of propofol at target concentrations varying between 2 and 6 μg/mL [35]. They did not perform a formal analysis of predictive performance, but reported that the Kataria model generally underestimated measured concentrations – mean measured concentrations at target concentrations of 2, 3, and 6 μg/mL were 2.4, 4.7, and 12.2 μg/mL respectively [35].

There are, as yet, no studies of the predictive performance of PK models for dexmedetomidine in children and no studies specifically investigating the predictive performance of pharmacokinetic models for propofol in children undergoing sedation.

Future Directions

Model Development and the Open TCI Initiative

TCI systems are in common use for propofol sedation and anesthesia in adult patients in >100 countries. A factor that is limiting the use of this technology in the pediatric population is the paucity of published data verifying the validity and accuracy of the current pediatric models in different settings and patient groups. One of the goals of the recently established "open TCI initiative" is to set up multicenter collaborations to investigate model performance at the extremes of age. It is hoped that this initiative will either verify the accuracy of current models or produce a better model for propofol for children. Once this is achieved, it is likely that the use of TCI technology for sedation and anesthesia in children will increase.[1]

Drug Interactions

Studies in adults over the past 15 years have made advances in our understanding of interactions between different classes of anesthetic agents. These interactions include pharmacokinetic interactions, in which the presence of one drug causes measured concentrations of another drug to be different from those expected, and pharmacodynamic interactions, in which the presence of one drug alters the clinical effects of another drug. It is clear that in adults, pharmacokinetic interactions are common among anesthetic agents, and usually result in higher than expected concentrations, and that pharmacodynamic interactions between hypnotics and opioids result in potent synergism for the sedative, anesthetic, respiratory, and cardiovascular effects of the hypnotic agents [12, 53–60].

Drover studied the pharmacodynamic interaction of propofol and modest doses of remifentanil in children undergoing endoscopy, and found that remifentanil reduced the target propofol concentration (Kataria age-adjusted model) required for tolerance of endoscopy from 3.7 to 2.8 μg/mL [48]. At present there is very little other published data concerning the magnitude and significance of anesthetic drug interactions in children. An understanding of this subject is important since it enables anesthesiologists to practice more safely, and sometimes to use these interactions for the benefit of patients. It is thus likely that much more work will be done on this subject, and that infusion and monitoring systems for children will display advisory messages based on real-time estimates of the interactions between coadministered agents.

Effect-Site Targeted TCI Systems

So far we have only discussed blood-targeted TCI systems, which attempt to achieve the target blood concentration set by the user, while the effect-site concentration follows passively with a time delay determined by the rate of blood-effect-site equilibration. When a suitable k_{eo} exists for a given drug, pharmacokinetic model and population group, then it can be used in conjunction with the pharmacokinetic parameters to "target" the effect-site instead of the blood concentration. Because the anesthetic drugs have their mechanism of action in the brain rather than the blood, effect-site targeting is intuitively more

[1] http://www.opentci.org/doku.php. Accessed 6 December 2008.

appealing than blood concentration targeting, and offers the potential or more rapid and precise control of the depth of sedation or anesthesia.

TCI systems operating in effect-site targeting mode manipulate the blood concentration to bring about the target (effect-site) concentration as rapidly as possible, by implementing an overshoot in blood concentration when the user increases the target effect-site concentration, and a blood concentration undershoot when the user decreases the target effect-site concentration. For effect-site targeting, the choice of k_{eo} value is critical, since it will determine the degree of overshoot or undershoot required. If the k_{eo} is too small for the patient and model, then an excessively large under- and overshoots will occur, and these may compromise patient safety.

Effect-site targeting has been implemented in commercially available TCI systems programmed with pharmacokinetic models suitable for use with propofol and remifentanil in adults. Unfortunately, there are differences in the way that effect-site targeting is implemented in the different pumps, resulting in significantly different infusion profiles for the same model in some patient groups [61]. It is hoped that the Open TCI initiative will be able to also resolve this controversy.

Although the commercially available TCI devices are generally also programmed with one or more pediatric propofol models, effect-site targeting has not been implemented for children. This is largely because there is currently no validated and generally accepted k_{eo} value for use with the pediatric propofol models. Munoz and colleagues recently used the time to peak effect methodology recommended by Minto et al. [62] to calculate k_{eo} values for use with the Paedfusor and Kataria models. Further studies are likely to be necessary to demonstrate the safety and benefit of effect-site targeting in children, before this technique is widely used in pediatric practice.

Patient-Maintained Sedation

A patient-maintained sedation (PMS) system is a TCI system in which the patient is able to alter (increase) the target (blood or effect-site) concentration by pressing a button on a handset. Safety is enhanced by having a preset lockout period during which further target increases are not allowed, and by having automatic decreases in target concentration if the handset is not operated within preset time limits [63–67]. These systems thus combine the benefits of TCIs (stable blood and effect-site concentrations) with the psychological and safety benefits of patient control. Although these systems have shown great promise in adult groups, they have not yet been investigated in children. It is highly likely that PMS systems suitable for use by children will be developed once issues regarding PK model validity have been addressed and safety of PMS has been demonstrated.

Closed Loop Control and The Future

Automated control systems are almost omnipresent in modern life and are accepted without question. They are found, for example, in many common household appliances, in autopilot systems on aeroplanes, and in systems controlling the flow of traffic on roads and on underground train systems. Computer systems capable of automatic control of anesthesia and sedation have been developed and tested in adults [68–75]. The benefits of closed loop control – automated accurate titration of the anesthetic dose, based on rapidly repeated automated measurements of the pharmacodynamic effect of the anesthetic agent – have yet to be demonstrated to translate into improved patient safety and better outcomes such as fewer incidents of inadequate or excessive sedation or anesthesia. An international collaboration between commercial and academic groups has been proposed, and a dialog with the FDA commenced, in an attempt to implement this technology into clinical practice [76]. Since the problems of dose titration for sedation and anesthesia apply to children as well as to adults, it is likely that this technology will one day be used to improve the accuracy of drug administration for sedation in children.

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Use of Complementary and Alternative Medicine in Pediatric Sedation

24

Yuan-Chi Lin

Introduction

Complementary and alternative medicine (CAM) describes any healthcare approach outside the area of conventional medicine. It is a group of diverse medical and health systems, practices, and products, and is commonly used in conjunction with conventional medicine.

The National Center for Complementary and Alternative Medicine groups these therapies into several domains (Table 24.1). It can come from a complete medical system of premise and practice, including homeopathic medicine, naturopathic medicine, traditional Chinese medicine, ayurveda, and Tibetan medicine.

Commonly utilized forms of CAM include biologically based practice, mind–body medicine, manipulative and body-based practice, and energy medicine. Biologically based practices of CAM employ the use of the substances from nature, including herbs, nutrition, vitamins, and dietary supplements. Mind–body medicine involves a variety of techniques designed to enhance the mind's capacity to affect bodily functions and symptoms. Some examples of mind–body medicine include meditation, biofeedback, relaxation, guided imagery, prayer, and music therapy. Manipulative practices are based on manipulation and movement of the body. These include massage, chiropractic, or osteopathic manipulation. Energy medicine employs the use of energy fields. Some examples include acupuncture, qi kong, reiki, and therapeutic touch.

Use of CAM in the pediatric population is increasing in popularity. In the United States, approximately 38% of adults and 12% of children currently use some form of complementary medicine [1]. The surgical environment is one in which CAM has become particularly popular with pediatric patients, families, and healthcare professionals. Pediatric patients require sedation more often than adults for medical procedures. These children are at higher risk for respiratory depression and life-threatening hypoxia. Periprocedure anxiety is directly related to fear, unfamiliar environments, and of loss of control. CAM can be used as a noninvasive modality for decreasing patients' anxiety and assisting with sedation.

Music

Music has been used for healing purposes through the ages. It is recognized as a safe, inexpensive, and effective anxiolytic adjunct to medical procedures. Music therapy employs the use of experiencing or making music for therapeutic purposes. It can serve as an adjuvant therapy in critical ill patients. In a randomized controlled trial, ten critically ill patients were allocated to music or no-music group. The

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Table 24.1 Major types of complementary and alternative medicine

Whole medical systems
Homeopathic medicine
Naturopathic medicine
Traditional Chinese medicine
Ayurveda
Tibetan medicine
Biologically based practices
Herbal products
Nutritional supplements
Vitamins
Dietary supplements
Mind–body medicine
Meditation
Biofeedback
Relaxation
Guided imagery
Prayer
Music therapy
Tai chi chuan
Manipulative practices
Chiropractic manipulation
Massage
Osteopathic manipulation
Energy medicine
Acupuncture
Qi kong
Reiki
Therapeutic touch

Source: Data from NCCAM, National Institutes of Health, Bethesda, MD

music group received a special selection of slow movements from Mozart's piano sonatas, which had been analyzed for compositional elements for relaxation. The music was delivered for 1 h via headphones, where the control subjects wore headphones without music. Music application was shown to significantly reduce the amount of sedative medication needed to achieve a comparable degree of sedation. In those receiving the music intervention, plasma concentrations of growth hormone increased, whereas those of interleukin-6 and epinephrine decreased. The reduction in systemic stress hormone levels was associated with a significantly lower blood pressure and heart rate. Music may exert its sedative effects by a neuro-humoral pathway involving interactions between the hypothalamo-pituitary axes with the adrenal medulla via mediators of the unspecific immune system [2].

The use of intraoperative music in awake patients decreases patient-controlled sedative and analgesic requirements. A randomized controlled study of 35 adults undergoing urologic procedures with spinal anesthesia and patient-controlled intravenous propofol sedation randomly assigned patients to intraoperative music via headset or to no intraoperative music. The patients in the music group required significantly less propofol for sedation than patients in the control group [3]. A randomized controlled study of 43 adults undergoing lithotripsy treatment of renal or ureteral calculi and receiving patient-controlled intravenous opioid analgesia also randomly assigned patients to either a music or a no-music group. The patients who listened to music had a significant reduction in alfentanil requirements [3]. By using self-report validated behavioral and physiological measures of anxiety, 93 adult patients were evaluated before, during, and after surgery. Patients who listened to music of their choice during the preoperative period reported less anxiety [4].

A randomized controlled trial of 70 children undergoing surgical procedures indicated that children are less anxious and show increased compliance during induction when exposed to a single care provider in a dimmed, quiet operating room with background music [5]. A study of 123 children was randomly assigned into one of three groups: interactive music therapy, oral midazolam, and a control group. The children who received midazolam were significantly less anxious during the induction of anesthesia than the children in the music therapy and control groups. There was no difference in anxiety during the induction of anesthesia between children in the music therapy group and children in the control group. Music therapy may be helpful on separation and entrance to the operating room, depending on the therapist; however, it does not appear to relieve anxiety during the induction of anesthesia [6].

Sixty pediatric patients receiving either chloral hydrate or music therapy for electroencephalography testing revealed that music therapy may be a cost-effective, risk-free alternative to pharmacological sedation [7]. There has been reports of a high success rate when utilizing music for pediatric patients undergoing computerized tomography scans, echocardiograms, initiation of intravenous

lines, and electroencephalograms. Music therapy is a cost-effective intervention for most pediatric facilities [8]. It can be used as an adjuvant therapeutic measure in pediatric sedation.

Hypnotherapy

Hypnotherapy is the induction of a trance-like state to facilitate relaxation of the conscious mind. The hypnotic trance is neither a sleep state nor a state of unconsciousness. It is a state of altered consciousness in which attention can be focused on some things to the exclusion of others. Relaxation, immobilization, and altering or abolishing painful stimuli are frequently seen with hypnosis. A study of 49 embolization procedures on 30 patients utilizing medical hypnosis revealed that 45 of the procedures were successfully performed using hypnosis [9].

Faymonville et al. did a study of positron emission tomography in 11 healthy volunteers to identify the brain areas in which hypnosis modulates cerebral responses to a noxious stimulus. Hypnosis decreased both pain sensation and the unpleasantness of noxious stimuli. Noxious stimulation caused an increase in regional cerebral blood flow in the thalamic nuclei and anterior cingulate and insular cortices. The hypnotic state induced a significant activation of a right-sided extrastriate area and the anterior cingulate cortex. The interaction analysis showed that how the activity in the anterior cingulate cortex was related to pain perception and unpleasantness was different from the hypnotic state than in control situations. Both intensity and unpleasantness of the noxious stimuli were reduced during the hypnotic state [10].

Lang et al. did a randomized study of 236 women referred for large core needle breast biopsy to receive standard care, structured empathic attention, or self-hypnotic relaxation during their procedures. The study demonstrated that hypnosis can be successfully integrated to core needle biopsy for the diagnosis of breast cancer. The adjunctive use of hypnosis by trained members of the procedure team resulted in substantially less anxiety and a reduction in pain, compared to two other randomized conditions: routine care and sympathetic assistance. After more than an hour, the hypnotic analgesia was clearly superior to that obtained in standard care or the nonspecific empathy conditions [11].

A study explored the use of hypnosis for pain and anxiety management in six colonoscopy patients who received a hypnotic induction and instruction in self-hypnosis on the day of their colonoscopy, compared to 10 consecutive patients who received standard care. Hypnosis appeared to be a feasible method of managing anxiety and pain associated with colonoscopy, reduced the need for sedation, and may have other benefits, such as reduced vasovagal events and recovery time [12].

Ghoneim et al. did a randomized controlled trial of 60 patients to evaluate the usefulness of tape-recorded hypnosis instruction on perioperative outcome in surgical patients. The hypnosis group received an audio tape to listen to daily for the immediate preoperative week. The controlled group did not receive a tape. Anxiety was reduced before surgery by means of the audio tape containing hypnotic instructions, and there was an increase in the incidence of vomiting [13]. Balini et al. studied 46 patients undergoing percutaneous transluminal coronary angioplasty of the left anterior descending coronary artery. They were randomized to receive medication or hypnotic sedation during the procedure. The increase in cardiac sympathetic activity associated with balloon inflation and myocardial ischemia during percutaneous transluminal coronary angioplasty of the left anterior descending coronary artery was selectively eliminated by hypnosis but not by drug sedation [14].

A meta-analysis performed on 18 controlled trials suggested that the addition of hypnosis substantially enhanced treatment outcome. The average client receiving cognitive-behavioral hypnotherapy showed greater improvement than at least 70% of clients receiving nonhypnotic treatment. Hypnotherapy enhances the effects of cognitive-behavioral psychotherapy, including anxiety, insomnia, pain, and obesity [15].

Hypnotherapy is one of the oldest forms of psychotherapy. It encourages the patient to use his or her imagination to improve health and

health behaviors. While most of the current research is on its use in the adult population, hypnotherapy may be integrated into pediatric sedation in the future.

Guided Imagery

Patients who undergo sedation usually experience some fear and apprehension about their procedures. Guided imagery is a simple, low-cost therapeutic tool that can help counteract these feelings. A randomized controlled trial of 130 patients underwent elective colorectal surgical procedures. They were assigned to receive either routine perioperative care or listen to guided imagery tapes for 3 days before their procedures, during the periprocedure period, and for 6 days after the intervention. The patients in the guided imagery group experienced considerably less preoperative and postoperative anxiety and pain, and required nearly 50% less narcotic medications than patients in the control group [16].

Guided imagery was successfully utilized in 56 patients undergoing radiology interventional procedures. They were enrolled in a standardized protocol with script-guided imagery to produce a state of self-hypnotic relaxation. Each of the patients developed an imagery scenario. Although there were common trends in the chosen imagery, such as nature, travel, family, home, and personal skills, the chosen topics were highly individual. This variable made prerecorded tapes or provider-directed imagery unlikely to be equally successful [17].

Anodyne imagery technique consists of conditioned relaxation, induction of a trance state, and guided processing of the patient's internal imagery. A study involved 100 patients undergoing interventional radiologic procedures. Anodyne imagery eased patients' anxiety and fears and reduced the amount of midazolam and fentanyl used during interventional radiologic procedures, possibly improving procedural safety and augmenting the speed of recovery [18].

Guided imagery technique can produce analgesia and anxiolysis. Though the technique is highly individualized, it has a potential to be integrated into pediatric sedation in the future.

Acupuncture and Related Techniques

Used for over two millennia, Acupuncture is one of the oldest medicinal practices in the world. It is part of traditional Chinese medicine. Since its reintroduction in the United States in the early 1970s, acupuncture has become a widely used complementary medical therapy, used to maintain and restore health through the stimulation of acupuncture points by the insertion of hair-thin needles through the skin. Acupuncture promotes the flow of "qi," which is equivalent to energy. Endogenous opioid peptides in the central nervous system play a major role in mediating the effect of acupuncture [19]. Several acupuncture-related techniques, including electro-acupuncture, moxibustion, cupping, acupressure, and auricular therapy, are commonly applied. Complications from acupuncture treatment are rare.

Acupuncture can be used to assist upper endoscopic and colonoscopy procedures. In a study of 106 patients, those receiving midazolam rated the procedure as slightly less troublesome than those receiving acupuncture. Oxygen saturation, blood pressure, and heart rate were significantly lower in patients receiving midazolam [20]. In a randomized controlled trial of 55 patients received colonoscopic examination with either electro-acupuncture analgesia or meperidine analgesia, the analgesic effect of both groups was the same. The electro-acupuncture group has fewer side effects, particularly in regard to dizziness. Serum concentration of beta-endorphin in both groups showed similar trends of change during colonoscopy. Changes in serum concentration of epinephrine, norepinephrine, dopamine, cortisol, and beta-endorphin were also similar between these two groups [21]. Another study of 30 patients undergoing colonoscopy was randomized to receive acupuncture, sham, or no acupuncture. Midazolam was used for sedation for all three groups. The acupuncture group experienced less pain and required less midazolam than the other two groups. The demand for sedative drugs during colonoscopy was decreased through the use of acupuncture by reducing the discomfort and anxiety of the patients [22].

In a study of 55 patients undergoing lithotripsy procedures, patients were enrolled into either an acupuncture or a sham group. In the acupuncture group, patients had less preprocedural anxiety and required less intraprocedural analgesia [23]. Another study involving 35 patient undergoing lithotripsy procedures showed that electroacupuncture was an effective method for inducing sedation with analgesia without any demonstrable side effects [24].

Acupressure on the Extra-one, EX-HN3, (Yin-Tang) acupuncture point is effective in producing sedation. The Extra-one, EX-HN3, (Yin-Tang) acupuncture point is located on the forehead, at the midpoint between the eyebrows (Fig. 24.1). Acupressure over this point produces analgesic and sedative effects. A study of 52 children undergoing endoscopic procedures was randomized to receive acupressure bead intervention either at the Extra-one (Yin-Tang) acupuncture point or at a sham point. Anesthetic techniques were standardized and maintained with intravenous propofol infusion. Children receiving the acupressure on the Extra-one (Yin-Tang) point experienced reduced anxiety. There were no significant changes in Bispectral Index values between the groups, and the total intraprocedural propofol requirements did not differ between them. Acupressure bead intervention at the Extra-one (Yin-Tang) acupuncture point reduced preprocedural anxiety in children undergoing endoscopic procedures, however [25]. A study involving 22 healthy female volunteers was randomized to receive acupressure on either the Extra-one (Yin-Tang) point or a sham point. Acupressure at the Extra-one (Yin-Tang) point significantly reduced needle insertion pain compared to acupressure at the sham point. Acupressure at the Extra-one (Yin-Tang) acupuncture point significantly reduced the low frequency/high frequency ratio of heart rate variability responding to needle insertion. This implies a reduction in sympathetic nervous system activity [26].

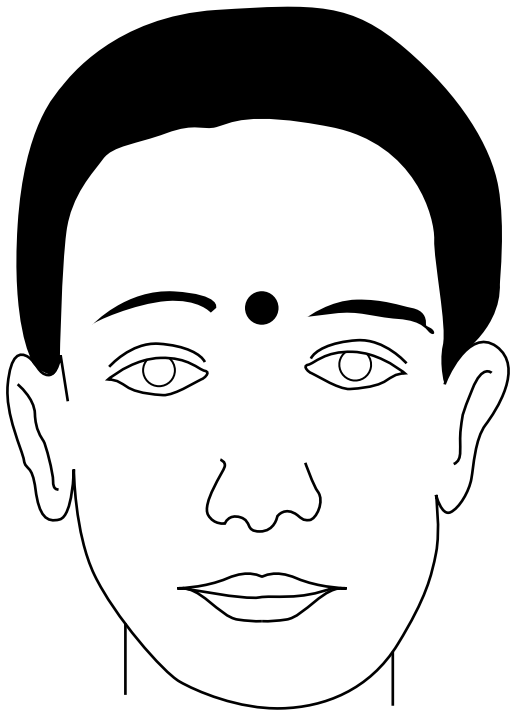

Fig. 24.1 Extra-one, EX-HN3, (Yin-Tang) acupuncture point locates on the forehead, at the midpoint between the eyebrows

A crossover study of volunteers indicated that acupressure on the Extra-one (Yin-Tang) acupuncture point can significantly reduce bispectral index values and verbal stress scores [27, 28]. In a randomized controlled trial of 48 volunteers, 5 min of acupressure on the Extra-one (Yin-Tang) acupuncture point significantly reduced the EEG spectral entropy values [29]. A randomized trial of 61 parents indicates that acupressure at the Extra-one (Yin-Tang) acupuncture point can have anxiolytic and sedative effects on parents in the preoperative holding area before their children's surgery [30].

Ear acupuncture, also known as auricular therapy (Fig. 24.2), is based on the principles of Traditional Chinese Medicine. It is practiced as a sole treatment or in conjunction with body acupuncture therapy, and is an effective treatment for acute anxiety. Ear acupuncture can decrease preoperative anxiety in adults undergoing outpatient surgery [31]. A study of 67 patients undergoing dental extraction compared the efficacy of auricular acupuncture, intranasal midazolam, placebo acupuncture, and no treatment for reducing dental anxiety. Patients having dental extractions were randomized to one of four groups: auricular acupuncture, placebo acupuncture, intranasal midazolam, and a

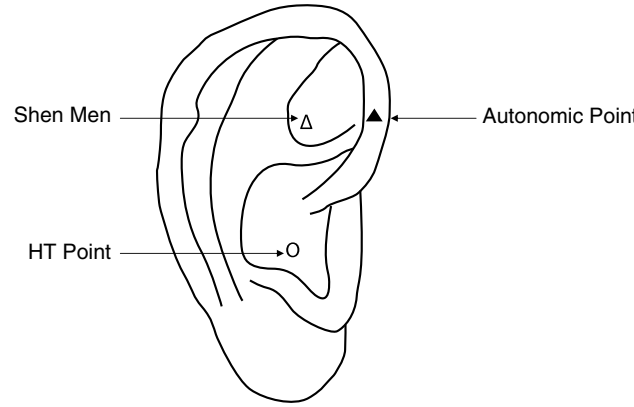

Fig. 24.2 Location of auricular acupuncture points

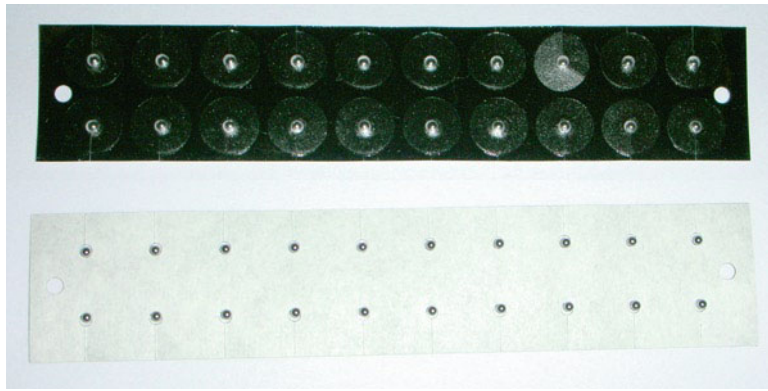

Fig. 24.3 Auricular acupressure press pellets, 1.2 mm diameter stimulating press pellets, are made from stainless steel

no-treatment group. Anxiety was assessed before the interventions, after 30 min, and after the dental extraction. The auricular acupuncture group and the midazolam group were significantly less anxious at 30 min compared to patients in the placebo acupuncture group. Patient compliance assessed by the dentist was significantly improved if auricular acupuncture or application of intranasal midazolam had been performed [32].

Auricular acupuncture points may be stimulated for a longer period of time by using ear seeds or ear tacks. Ear seeds can be small seeds from the dry Vaccaria plant or can be made from stainless seed. These seeds are held in place on the ear with a small piece of adhesive tape (Fig. 24.3). Auricular acupressure is an effective treatment for anxiety during ambulance transport. In a study of 36 patients who required ambulance transport to medical facilities, patients were randomized to receive auricular acupressure at the relaxation point or at a sham point. Patients in the auricular acupressure group reported significantly less anxiety than patients in the sham group on arrival to the hospital [33]. Another randomized controlled trial of 38 patients with acute hip fractures received either bilateral auricular acupressure or the sham control during ambulance transport. Patients in the true intervention groups had less pain and anxiety and lower heart rates on arrival at the hospital [34].

Acupressure is the application of pressure to the acupuncture points with the finger, which can achieve significant clinical effects. In a double-blinded design study of 60 minor trauma patients, they were randomly assigned into one of the three groups, true acupressure, sham acupressure, and

no acupressure. The group of patients who received true acupressure experienced significantly less pain, anxiety, and had a lower heart rate, and reported greater satisfaction, than the other two groups [35].

Postsedation nausea and vomiting is a significant problem that occurs frequently in the postsedation recovery care unit. It can cause electrolyte imbalance, delay discharge and other complications. Schlager et al. [36], using low level of laser stimulation of the PC6 acupuncture point (Fig. 24.4) in children undergoing strabismus surgery, found that the intervention significantly decreased postoperative vomiting. Chu et al. [37] applied acupressure with acuplaster to BL-10, BL-11, and GB-34 acupuncture points as prophylactic treatment for postoperative vomiting in children undergoing strabismus surgery. The investigators randomized a total of 65 children between ages of 3 and 14 years into a placebo or an acuplaster group. They found that significantly fewer patients developed postoperative vomiting in the acuplaster group than in the placebo group during the first 24 h following surgery.

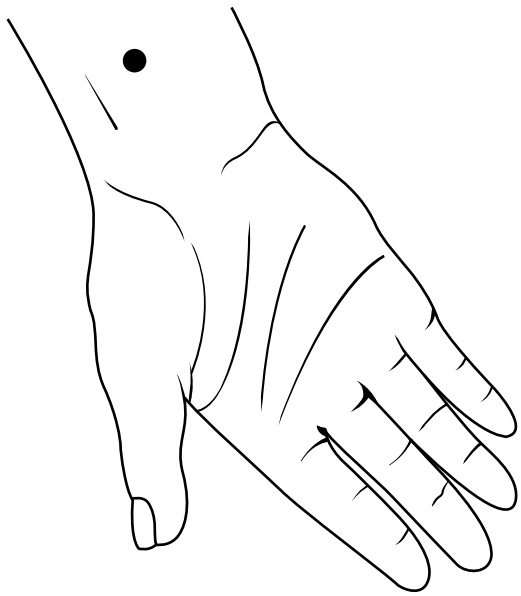

Fig. 24.4 PC6 acupuncture point locates on the anterior forearm, three-finger breadth proximal to the transverse wrist crease, between the tendons of palmaris longus and flexor carpi radialis muscles

Schlager et al. [38] applied acupressure to acupuncture points in the hand 30 min before induction and kept the acupressure in place for 24 h in a group of children undergoing strabismus surgery. They found children in the acupressure group had a significantly lower incidence of vomiting as compared to the placebo group. Somri et al. [39] compared the antiemetic effect of P6 acupuncture with ondansetron and a placebo in a group of children receiving dental surgery. They found a significant decrease in the number of patients who vomited and also in the total number of vomiting episodes in two treatment groups as compared with the placebo group. There was no difference between the acupuncture and ondansetron groups.

Rusy et al. [40] used electrical stimulation of acupuncture point P6 as a prophylactic postoperative nausea and vomiting treatment for children undergoing tonsillectomy with or without adenoidectomy. The investigators also found that children who received true electrical stimulation at acupuncture points PC6 had significantly less postoperative nausea and vomiting. Butkovic et al. [41] compared the use of laser acupuncture and metoclopramide in preventing the development of postoperative nausea and vomiting. The investigators found that bilateral laser acupuncture PC6 stimulations are as effective as metoclopramide in preventing the development of postoperative nausea and vomiting in children.

Kabalak et al. [42] applied transcutaneous electrical acupuncture point stimulation utilizing skin surface electrodes. They applied 20 Hz and 10 mA for 5 min to the P6 acupuncture points. It was as effective as ondansetron in preventing postoperative vomiting following pediatric tonsillectomy. A meta-analysis of the acupuncture points stimulation effect on postoperative nausea and vomiting in children indicates that acupressure and acupuncture are as effective as medication in reducing postoperative vomiting in children [43].

Most of the available studies involve the adult population, rather than pediatric patients. Evidence-based medical research has indicated that acupuncture and related techniques can be used for analgesic, anxiolytic, and sedative effects. It is

very effective in prevention and treatment of periprocedure nausea and vomiting [44]. It is estimated that there are more than 20,000 licensed acupuncture providers in the United States among them 3,000 physicians perform acupuncture as part of their medical practice. Acupuncture and related techniques can be used in conjunction with conventional therapy for sedation and prevention and can ease discomfort after the procedure.

Is Sucrose a Sedative or Analgesic in Infants?

Sweetening agents have been recommended in position statements and consensus documents for procedural pain management in neonates. Sucrose is reported to stimulate the lingual receptors and initiate the release of endogenous opioids [45, 46]. A randomized study was performed on 113 healthy full-term newborns whose heels were pricked for the Guthrie test to detect phenylketonuria. The babies were randomized into four groups: one receiving 2 mL of 30% sucrose, the second 10% glucose, the third 30% glucose, and the fourth distilled water. Thirty percent sucrose is superior to 10 and 30% glucose solutions in relieving pain [47].

Screening for retinopathy of prematurity (ROP) in infants is an acknowledged painful procedure. 0.2 mL of sucrose 24% has been shown to reduce the behavioral and physiological pain responses [48].

Johnston et al. studied 85 preterm infants between 25 and 34 weeks postconceptual age. They were randomly assigned to oral sucrose and/or simulated rocking, 15 min before a routine heel stick procedure. When 0.05 mL of 24% sucrose was placed on the anterior surface of the tongue just prior to the lancing of the heel, the pain was attenuated in preterm infants [49]. A single-blind randomized crossover study examined 90 preterm neonates undergoing heel-lancing procedures. The sensorial stimulations from skin-to-skin contact that include tactile and olfactory sensations from the mother, are sufficient to decrease pain response in premature neonates. Other stimulations like rocking, sucking, and music were also efficacious for neonatal sedation [50]. There is strong evidence to support sucrose for minor invasive procedures in neonates [51].

Conclusion

Sedation for pediatric procedures can be distressing for children and their families. Studies related to using CAM, nonpharmacological methods for reducing anxiety and improving cooperation, may avoid the adverse effects of sedation. A Cochrane review assesses 17 trials and the effects of CAM nonpharmacological interventions in assisting induction of anesthesia in children reducing their anxiety or distress or increasing their cooperation. Eight trials assessed parental presence. Parental presence was significantly less effective than midazolam in reducing children's anxiety at induction. In children undergoing hypnosis, there was a nonsignificant trend toward reduced anxiety during induction compared with midazolam. Children of parents having acupuncture compared with parental sham-acupuncture were less anxious during induction and more cooperative. Presence of parents during induction of general anesthesia does not reduce their child's anxiety. Promising CAM nonpharmacological interventions include parental acupuncture, clown doctor, hypnotherapy, low sensory stimulation, and handheld video games [52].

Most medical procedures increase the child and family's fears and anxiety. Insufficient treatment of pain and anxiety can cause cardiovascular strain and restlessness, possibly jeopardizing the success of the procedure. Pharmacologic oversedation can provoke respiratory and cardiovascular depression, thereby increasing the procedural risks and delaying the patient's recovery. Pediatric sedation should be individually tailored to each child's personal situation. CAM interventions are supplementary measures that can help children and their families adapt to the hospital environment. They can be integrated as part of pediatric sedation procedures. It may not be the sole therapy, but CAM can be used in conjunction with conventional medical therapies to assist with sedation and decrease patients' pain and anxiety.

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The Future of Pediatric Sedation

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James R. Miner

Over the past 2 decades, pediatric sedation outside of the operating room has evolved rapidly and is an important part of the care of children. It is now an area of interest, research, and clinical practice which encompasses multiple specialties. Policies, procedures, and guidelines have been created worldwide by specialty organizations and even governmental agencies, all designed to maximize safety and outcome. Clinical research continues in efforts to further our knowledge of sedation practice, predictors of adverse outcome, and improve safety. There still remain many opportunities to optimize the safe practice of pediatric sedation as well as improve the efficiency and efficacy of its implementation [1].

Often, when we look for advances in sedation, we look to new agents to improve our practice. The perfect sedation agent would allow the physician to provide adequate analgesia and amnesia of the painful sedation, have a precisely controllable duration of action, and then quickly have complete recovery without any adverse events. Unfortunately, this agent does not currently exist, and we must adjust the protocols that we have to come as close as possible to this goal.

This concluding chapter will summarize the progress that has already been made and reflect on the opportunities and ongoing needs for advancing the field of pediatric sedation. The future of pediatric sedation will benefit from our ability to more accurately target, and achieve the optimal level of sedation, analgesia, and amnesia needed for a given procedure. Advances in sedation will require that we improve our ability to proactively identify, anticipate, prepare for and treat adverse events. The important areas which remain to be explored and advanced will be reviewed.

The Optimal Level of Sedation

Outcome Assessment and Standardization of Adverse Event Identification and Documentation

From the patient's perspective, a swift return to preprocedure mental status in the setting of having achieved adequate amnesia and analgesia represents a good outcome measure of a successful sedation. To achieve this outcome measure, the sedation provider would need to achieve a deep level of sedation in order to avoid the recall associated with lighter levels [2–4]. The desire to balance patient satisfaction with safe outcome requires that the provider anticipate that at the deepest levels of sedation, patients are at the highest risk for complications. These risks are most prone to occur within 3–20 min of receiving intravenous (IV) sedatives and when noxious stimuli are removed (immediately after the procedure) [3].

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In terms of an assessment of the risk to the patient, however, the presence and nature of any adverse events that occurred during the sedation procedure are a good measure of the procedure's outcome. Adverse event rates for procedural sedation outside of the operating room (OR) have been described to range from 2.5 to 7.7% [5–10], but the actual rate depends on what is considered to constitute an adverse event, and it has varied among studies. The outcomes of sedation to a deeper level than intended, hypoxia, the need for assisted ventilations, clinically significant hypotension, aspiration, and endotracheal intubation are widely accepted indicators of adverse events during a sedation procedure.

Ironically, the very indicators that we use to compare and assess sedation outcomes are not always clearly defined nor accepted. For example, the occurrences of hypoxia and hypotension are identifiers which have no standardized definition. A review of the published sedation literature indicates that the definitions of hypoxia range from a 5 to 20% drop in oxygen saturation and hypotension is defined as a 0–30% deviation from either the patient's presedation vital signs or from established normal values. Without clearly defined, standardized, and objective identifiers of adverse events, it is difficult to evaluate and compare sedation outcomes in the literature.

A recent set of recommendations [11] has advocated for the adoption of objective, standardized definers which could be applied not only to clinical studies, but also to quality assurance programs. These recommendations advocate that the need to "intervene" is an easily identifiable and objective identifier of the occurrence of an adverse or noteworthy event. This new benchmark would be robust to clinically insignificant events, but sensitive to events which are not necessarily captured with physiologic monitors. This benchmark would identify events which require physician intervention with the patient in order to avoid, treat, or resolve complications. This advance in research may help identify risk factors associated with the need for intervention and may ultimately highlight factors, predictors, and protocols which may be associated with adverse events. Identifying risk factors may allow us to refine our pediatric sedation techniques and guide our training and credentialing process.

Defining Depth of Sedation

The Sedation Continuum is another topic of interest [12]. Clinical outcomes, policies, guidelines, and recommendations are usually founded on the depth of sedation and associated risks. For example, which provider/specialist is qualified to administer deep sedation has become a controversial topic. The specialty societies worldwide, the Center for Medicaid and Medicare Services in the United States as well as the government sponsored health services abroad, have all weighed in with different opinions and guidelines [9, 13–22; http://guidance.nice.org.uk/cg112]. The basic tenet of this controversy, the sedation continuum, is founded on a relatively subjective scoring system: The assessment of a patient's response to verbal, tactile, and painful stimulation in order to define a depth of sedation. The tenet of the sedation continuum is that the depth of sedation is fluid and a patient can fluctuate between levels. There are limitations to this scoring system: It is subjective and not always a feasible method of assessment. Continuous monitoring of this continuum is not always possible, appropriate, or safe, particularly when the sedated patient is far removed from the sedation provider (magnetic resonance imaging studies) or undergoing a procedure which discourages patient response (angiography) [23].

Other sedation scales have been proposed in efforts to minimize the subjective component of the scoring process [24]. None, however, have eliminated the subjective contribution. Rather, these markers are associated with increasing levels of sedation and respiratory depression and are not accurate identifiers of procedural success, patient recall, and the incidence of adverse events [25]. In order to advance our ability to detect adequate sedation, more precise measures of the depth of sedation must be developed [1, 23, 26].

Green and Mason have advocated a reformulation of the sedation continuum. Instead of basing the scale on subjective or semi objective criteria, scales based on objective physiologic monitoring would be devised. The reformulated sedation continuum would be based on an objective means of assessing and stratifying sedation

risk. The tool would be identified as the Objective Risk Assessment Tool for Sedation (ORATS) [26] (Figure 4.4). The ORATS tool would be used in conjunction with a Comfort Assessment Tool for Sedation (CATS) which reconfigures the existing sedation continuum to reflect and follow the degree of comfort [26]. The standardization of adverse events, using the aforementioned "intervention based" approach and the application of a new tool to assess depth of sedation, will be an important step to supplement our assessment of the depth of sedation and associated risks at each level [11].

"Consciousness" Monitoring as an Indication of Sedation Depth

Amnesia and analgesia are important to our patients. Without a subjective "amnesia" monitor, we tend to target a deep level of sedation in order to minimize the risk of recall. The deeper the level of sedation achieved during procedural sedation, however, the higher the rate of respiratory depression, and therefore the higher the risk of adverse events [2]. Ideally, the optimal sedation encounter would ensure amnesia and analgesia with minimal risk of respiratory depression and other adverse events.

To date, there is no means of ensuring amnesia during sedation [27]. Currently, a patient's level of sedation is mainly determined through interactive, subjective assessments which integrate the physiological vital signs with a patient's response to verbal or painful stimulation. Factors such as eye opening, response to voice, and response to pain are often used to extrapolate depth of sedation and likelihood of amnesia. These factors, although likely to be associated with the progression toward deeper levels of sedation and associated adverse events, do not predict recall or analgesia. This technique is not always successful. Patients who appear alert may actually have no recall following a painful procedure with propofol [25]. As we advance our knowledge of sedation, it will be important to determine the presence of procedural amnesia in order to guide us in our titration of sedation while minimizing the risk of adverse outcome.

The future of sedation would benefit from a physiological monitor that accurately follows "depth" of sedation and likelihood of amnesia. The Bispectral Index (BIS) is a monitor which was originally introduced to monitor the depth of anesthesia. It is a noninvasive monitor which monitors electroencephalogram (EEG) activity from adhesive leads which are placed on the forehead. Using a 1–100 analog score, BIS denotes a number which is intended to reflect brain activity and provide an objective monitor of depth of anesthesia [2–4, 28]. Although initially hoped to be a monitor which could follow depth of sedation and provide a surrogate marker for risk of patient recall, BIS is not an accurate nor reliable for most sedation [28–30]. It often defaults to high values in sedated patients when there is motion artifact, limiting its utility for pediatric sedation. Currently, its practical application as a monitor for depth of sedation is controversial, and its use remains investigational [2–4]. The future of sedation would benefit from the development of an objective monitor which would quantify the level of consciousness and improve the precision in achieving adequate sedation and amnesia without progressing to a deeper level of sedation [2].

Assessment of Oxygenation, Respiration, and Identification of Hypoxia

Pulse Oximetry

A patient's oxygen saturation is typically monitored during procedural sedation using pulse oximetry and is a Standard of Care for most specialties who provide sedation [1, 4, 9, 17, 31–33]. There are limitations: A variable lag time between the onset of hypoventilation or apnea and a change in oxygen saturation, especially in patients who receive supplemental oxygen [34–36].

Pulse oximetry measures oxygenation, and not ventilation. A patient breathing supplemental oxygen may not exhibit changes in their oxygen saturation until several minutes after the onset of hypoventilation. In a patient receiving supplemental oxygen, it can be a late sign of hypoventilation

[37, 38]. It is possible that in the future pulse oximetry may be replaced or supplemented with newer technology that uses near-infrared spectroscopy to monitor nonpulsatile signals of arterioles, capillaries, and venules, a indication of cerebral oxygenation. Unlike conventional pulse oximetry, which monitors the pulsatile signal component reflecting arterial circulation, cerebral oximetry can be reliable in low perfusion states, shock, and cardiac arrest situations. The role of cerebral oximetry has yet to be validated: A recent procedural sedation study, which demonstrated poor correlation between cerebral oximetry, pulse oximetry, and capnography [39]. In this study, 100 children ages 9 months to 18 years were sedated with various agents (ketamine, fentanyl, pentobarbital, dexmedetomidine, or propofol). Changes in rSO_2 occurred in 2.1% of patients and were associated with changes in SpO_2 23% of the time and changes in end-tidal CO_2 29% of the time. Only a minority of hypoxic episodes resulted in a decrease in rSO_2, while the majority of changes in rSO_2 occurred in the absence of changes in cardiorespiratory parameters. Although rSO_2 appears to be a more sensitive measure of cerebral oxygenation than pulse oximetry, there is no clear rSO_2 threshold under which clinically significant brain hypoxia occurs [40]. Future studies need to be directed towards determining whether there is any application for this technology.

Capnography

Capnography is a monitor designed to follow ventilation. Changes in the capnogram shape can demonstrate changes in ventilation, while changes in end-tidal CO_2 (the maximum CO_2 concentration at the end of each tidal breath) can be used to estimate the severity of these changes, the response to interventions, and to quantify the degree of respiratory depression [41]. Large changes in the end-tidal CO_2 values and in the waveform shapes have been associated with respiratory depression in sedated patients [34, 36] and may allow earlier identification of possible hypoventilation than oximetry [34, 36]. Capnography can rapidly detect apnea, upper airway obstruction, laryngospasm, bronchospasm, and respiratory failure [42–44]. Capnography is more sensitive than pulse oximetry in identifying impending hypoxia in patients who are receiving supplemental oxygen [34, 36]. It is not currently known, however, whether earlier detection of hypoventilation has any impact on outcomes and the benefit of adding capnometry and oximetry to interactive monitoring remains unclear.

There has been a great deal of research in capnography during sedation. Currently, these findings are made through gross visual examination of the waveform and trends in the end-tidal carbon dioxide value. As research in this area continues, it is likely that these monitors will be used to detect subtle changes in respiratory effort and ventilator capacity that will be associated with both the depth of sedation and the need for airway interventions prior to the onset of an adverse event. With more precise capability to predict and lower the incidence of hypoxia, capnography may someday be incorporated into sedation practice as a Standard of Care monitor.

Risk Assessment in Balancing the Urgency for the Procedure with the Associated Risk of Sedation

The urgency of the patient's requirement for procedural sedation and the patient's current medical condition play an important role in determining the level of risk for adverse events that can be accepted for a procedure. A common tool used to assess the severity of a patient's underlying illness is the American Society of Anesthesiologists' (ASA) physical status classification system [45]. Most research in the area of pediatric sedation outside of the operating room has focused on physical status class 1 and 2 patients, and the risk of an adverse event in these patients is well known. The risk of adverse effects of procedural sedation is likely higher in patients who have physical status scores of 3 or 4 [43].

The urgency of a patient's need for the procedure for which one is being sedated is based on the nature of the problem that requires sedation. Emergent indications for procedures may include cardioversion for life-threatening arrhythmias, reduction of fractures or dislocations with soft-tissue or vascular

compromise, or intractable pain or suffering. Not all procedures are emergent, and the remainder must be triaged to either urgent, semiurgent, or elective/nonurgent. The degree of urgency often guides the acceptable level of risk for adverse events for procedural sedation. Patients with an emergent need for sedation are unlikely to benefit from a delay in the procedure if they have eaten food prior to the procedure [46], whereas a patient with a nonurgent need for sedation is much more likely to benefit from such a delay.

Other than the ASA physical status score, the patient's current medical condition, NPO status, and the assessment of the patient's airway and respiratory status, there has not been a great deal of investigation into the risk factors for adverse events that can be identified before the procedure has begun. As our knowledge of procedural sedation increases, the risk of adverse events subsequent to specific procedures and in patient with a variety of medical conditions needs to be established. Once these data are available, this information, along with the risk of adverse events associated with various depths of sedation, can be used to decide on the best level and timing for procedural sedation for each given procedure and can allow us to better tailor sedation to a given circumstance for a patient's specific medical situation and sedation needs.

Analgesia, Prophylaxis, and Avoiding Conditioned Behaviors

Patients who present in pain would benefit from analgesics prior to initiating the sedation. The combination of sedatives and analgesics, however, may increase the likelihood of adverse outcomes [8, 47, 48]. The optimal method to treat procedural pain during sedation, and the degree to which it should be relieved, has not been determined. It is likely that patients who receive more preprocedural analgesia are more prone to respiratory depression during the sedation [48].

The determination of the optimal balance between pain management and safety is difficult and requires close assessment of the patient's ongoing pain. Future work should focus on improving our ability to provide analgesia without increasing the risk of adverse events. In those situations in which the procedure is successfully completed albeit some pain, it will be important to determine whether the inability to recall this painful experience, because of the amnestic effects of the medication, could have enduring, subversive, psychological effects.

Since pain is a subjective experience, our knowledge of a child's pain is achieved by patient report. Due to the limitations of communication with children, especially in younger children, the assessment of pain is often done simply by observation and many methods of assessing exist [49–59]. It has been found in numerous studies that healthcare providers consistently underestimate a child's pain, as do the child's parents (although the parents are usually closer to the child's rating than the healthcare providers) [60]. It is often difficult to distinguish a child's pain and agitation from distress due to the situation surrounding the pain. The physiologic measurement of pain remains beyond current capabilities, and there is no blood test or physical sign that can predict how much pain a patient experiences, leaving the situation more difficult in children than it is in adults. In the setting of repeated painful experiences, children will begin to recognize the activities of the event and develop conditioned behaviors related to upcoming painful events. The determination of which aspects of the pain response are most associated with changes in future pain behavior will guide us in modifying our sedation technique to reduce the risk of sensitizing the child to future painful procedures.

Training and Credentialing of Sedation Providers

Most of the data on procedural sedation are drawn from large academic centers with high sedation volumes. Sedation data from lower volume settings suggest that their outcomes are similar to that of busy nonacademic centers [61]. It is difficult to make conclusive comparisons regarding these two settings. Since many aspects of safe and effective procedural sedation rely on the interactive monitoring, experience, and the judgment of

the operator, such as his ability to recognize depth of sedation and ventilatory effort, it seems likely that less-experienced providers would experience a comparatively higher rate of adverse events. There is likely a minimal amount of experience required in order to bring a provider to the point where he can balance the sedation depth with the adverse event risk. Determining the point at which a provider can safely perform these tasks will be important in the determination of appropriate training for procedural sedation. At a national, state, and professional society level, there has been evolving interest and commitment to setting guidelines and standards for sedation delivery among healthcare professionals.

At a national level, the Joint Commission does not mandate specific credentialing for moderate sedation, but leaves it to the organizations to determine the necessary and needed training and skills. In an update on 7 July 2010, the Joint Commission reiterated that "the individuals who are 'permitted' to administer sedation are able to rescue patients at whatever level of sedation or anesthesia is achieved either intentional or unintentionally, e.g., when the patient slips from moderate into deep sedation or from deep sedation into full anesthesia. Each organization is free to define how it will determine that the individuals are able to perform the required types of rescue. Acceptable examples include, but are not limited to, ACLS certification, a satisfactory score on a written examination developed in concert with the department of anesthesiology, a mock rescue exercise evaluated by an anesthesiologist".

In the United States, some specialty organizations such as the American Dental Association (ADA) have released a policy statement which puts the onus of credentialing on the dental boards of each state. In their October 2007 Policy Statement on the Use of Sedation and General Anesthesia by Dentists, the ADA leaves the responsibility for credentialing in the hands of the individual states: "Appropriate permitting of dentists utilizing moderate sedation, deep sedation and general anesthesia is highly recommended. State dental boards have the responsibility to ensure that only qualified dentists use sedation and general anesthesia. State boards set acceptable standards for safe and appropriate delivery of sedation and anesthesia care, as outlined in this policy and in the ADA Guidelines for the Use of Sedation and General Anesthesia by Dentists" [18].

The ASA has been much more specific in making recommendations for training and credentialing. They issued a Statement on Granting Privileges For Deep Sedation To Non-Anesthesiologist Sedation Practitioners on 20 October 2010 [17]. It recommends that the nonanesthesiologist be able to bag-valve-mask ventilate, insert an oro/pharyngeal airway and laryngeal mask airway, and perform an endotracheal intubation. This should include a minimum of 35 patients, inclusive of simulator experience. Practitioners should be familiar with the use and interpretation of capnography. Deep sedation of children requires PALS and ACLS certification as well as separate education training and credentialing [62]. The ASA Statement recommends that non-anesthesiologists be proficient in advanced airway management for rescue when they deliver deep sedation. This proficiency and competency would be determined by the Director of Anesthesia Services of the facility in which the sedation is delivered [17]. In addition, the ASA specified that performance evaluation and a performance improvement program would be required for privileging–both of which would be developed with and reviewed by the Director of Anesthesia Services [17].

The topic of training, credentialing and privileging process of non-anesthesia specialists has become an area of debate. In response to the above ASA Statement, in July 2011 the American College of Emergency Physicians released a Policy statement entitled Procedural Sedation and Analgesia in the Emergency Department: Recommendations for Physician Credentialing, Privileging, and Practice [62]. This Policy iterated that the chief of the emergency medicine service at each institution will be responsible for establishing criteria for credentialing and recommending emergency physicians for sedation privileges. Sedation training should "focus on the unique ED environment".

The government has also issued guidelines via the Center for Medicaid and Medicare Services, and as recently as May 2010 and February 2011, updated the Hospital Anesthesia Services Condition of Participation 42 CFR 482.52 (a) [22, 63]. The ASA recognizes the Center for Medicare and Medicaid Services (CMS) as defining those qualified to administer deep sedation. The 2010 CMS guidelines limited deep sedation to be delivered only by an anesthesiologist, nonanesthesiologist MD or DO, dentist, oral surgeon, podiatrist, Certified Registered Nurse Anesthetist (CRNA), or Anesthesia Assistant (AA) [63]. These CMS guidelines towards nonanesthesia providers of sedation were revised in January 2011 in the PUB 100–07 State Operations Provider Certification which revises Appendix A for various provisions of 42 CFR 482.52 concerning anesthesia services [22]. These revisions were made in response to feedback from practitioners and allows the individual hospitals to establish their own policies and procedures with respect to the qualifications of analgesia providers and the clinical situations which distinguish anesthesia from analgesia. The policies must follow nationally recognized guidelines and can include guidelines of one or more specialty societies.

In response to the January 2011 update to the CMS guidelines [22], the American College of Emergency Physicians used their Policy statement of July 2011, entitled Procedural Sedation and Analgesia in the Emergency Department: Recommendations for Physician Credentialing, Privileging, and Practice to delineate who would be appropriate to deliver deep sedation [62]. The emergency medicine physicians, physician assistants, nurse practitioners and nurses could be credentialed to deliver sedation. Furthermore, the Policy acknowledges that the emergency medicine physician may commonly administer general anesthesia for specific situations in the emergency department (intubation, postintubation, procedures on intubated patients). It expands the role of the emergency physicians as well as emergency medicine nurses by condoning the capability of qualified ED nurses to "administer propofol, ketamine, and other sedatives under the direct supervision of a privileged emergency physician". The Policy also recognizes that there may be occasions whereby the emergency medicine environment may not lend itself to having a separate physician administer the sedative and another to perform the procedure: For these situations, the Policy states "Deep sedation may be accomplished by the same emergency physician both administering sedation and performing the procedure [62]."

California has taken the initiative to credential sedation care providers. Specifically, the California Board of Medicine recently sponsored and passed legislation (AB2637.Eng, Chap. 499) allowing the dental board to issue a dental sedation assistant permit after a minimum of 12 months of work experience. The permit allows the assistant to monitor conscious sedation or general anesthesia from noninvasive instrumentation. They may also add drugs, medications, and fluids to intravenous lines using a syringe [64].

At a state level, the New York State Department of Health has already recognized the importance of safe delivery of sedation in the office-based setting. In 2007, the state required that office-based surgery (OBS) be performed in an accredited setting. Expounding on this, on 14 July 2009, the state became more specific: any physician performing "office-based surgery" (OBS) must do so either in an Article 28 licensed hospital, ambulatory surgery center, diagnostic and treatment center; or in a private physician's office that is accredited. Accreditation may come from one of three organizations: The Joint Commission (TJC), Accreditation Association for Ambulatory Health Care (AAAHC), or American Association for Accreditation of Ambulatory Surgery Facilities (AAAASF).

In the future, it is very likely that other states will follow New York's lead and increase the vigilance and scrutiny of OBS which requires moderate to deep sedation. We anticipate that there will be increased requirements for accrediting outpatient facilities to perform moderate or deep sedation and to credential practitioners in those settings [65]. Outpatient clinics and providers will likely be held to the same standards as

hospital-based centers. This will further increase the need for standardized and effective practitioner training and assessment.

In general, all sedation care providers agree that sedation training, credentialing and privileging are important. There is a lack of consensus among the different specialties as to which specialty should be responsible for developing the sedation training programs as well as for credentialing the provider. One skill set required for the safe delivery of sedation, however, remains universally accepted: the ability to recognize and manage a compromised airway. This skill set will remain a critical and integral component of the training and credentialing process and would benefit from a standardized approach. A possible approach to facilitate and standardize the credentialing process would be to develop simulation training as an added tool to the didactic and hands-on experience. These simulators could develop scenarios that are specific for the specialty, patient population, and type of facility (office vs. hospital-based setting). They could also be used as a research tool to evaluate adverse events: By artificially creating an adverse event model, one could develop techniques to identify the contributing factors as well as ways in which to monitor, detect, and manage these occurrences. Such a model could also be used to train and assess the proficiency of providers. This model of training has long been in existence in the airline industry.

Flight simulation dates back to before World War I and has been used to train pilots and subsequently crew and air traffic controllers [66; http://www.faa.gov/about/initiatives/nsp/flight_training/bulletins/]. The roots of *Crew Resource Management* training in the United States are usually traced back to a workshop, *Resource Management on the Flightdeck* sponsored by the National Aeronautics and Space Administration (NASA) in 1979. This conference was the outgrowth of NASA research into the causes of air transport accidents. The research presented at this meeting identified human error aspects of the majority of air crashes as failures of interpersonal communications, decision making, and leadership. At this meeting, the label Cockpit Resource Management (CRM) was applied to the process of training crews to reduce "pilot error" by making better use of the human resources on the flightdeck [http://www.mercadodaaviacao.com.br/arquivos/17_04_2010_12_39_57_crm_evolution_-_faa.pdf].

The Federal Aviation Authority (FAA) as well as The National Aeronautics and Space Administration (NASA) have incorporated and mandated simulation training for credentialing, licensing, and continued education. The enactment of incidences which occur with low incidence, potentially so low that a pilot may never actually even experience the real-life scenario, offers the pilot the advantage to rehearse for such an occasion. These "rehearsals" could be as important to ensuring the safety of the passengers on an airplane as they are to the children that we sedate. Simulation models and training have already been implemented throughout the specialties for training purposes [67–76]. The importance of adopting sedation-directed simulation scenarios into the training and credentialing process still needs to be explored and will likely play an important role in maximizing safe practice [77].

Educating the Public

With recent publicity over the sedation-related deaths of celebrities (Anna Nicole Smith, Heath Ledger, Michael Jackson), the public awareness of sedation, the sedation agents (propofol, in particular), and the risk of mixing multiple sedatives is in the spotlight. The National Institute of Health has even published a three page Patient Education brochure entitled Conscious (Moderate) Sedation for Adults [78] in order to educate the layperson. In New York, as of 14 July 2009, patients can refer to www.nyhealth.gov to determine whether the OBS center that is using more than minimal sedation to perform a surgical or invasive procedure is accredited. Any practices which perform such procedures with more than minimal sedation and no accreditation are hence guilty of professional misconduct and disciplinary action. Patient awareness and scrutiny of sedation practice, including the agents, qualifications, and experience of providers, emergency preparedness, and outcome data should drive the field of pediatric sedation forward.

Developing the "Safety Culture" of Sedation: Implementing Safety Measures

Establishing a "safe culture" around sedation practice is important. Credentialing, standardizing the definition of adverse events, improving sedation delivery methods and techniques, introducing new sedatives, incorporating simulation into provider training, and using more objective means of identifying depth of sedation and associated risks are all important first steps. There are also new methods that could be adopted. Once again, the airline industry has been on the forefront of adopting and exploring new methods at ensuring safety. The industry has adopted the use of "check-lists" [79–82]. The airline industry, NASA, and FAA have been developing checklists since before World War II [79–82]. Checklists have begun to be adopted in the medical community as a means to foster active discussions and teamwork [83–86]. In 2009, a multiinstitutional, international group of eight hospitals published prospectively collected data on a total of 7,688 consecutive patients, before and after the adoption of a 19-item Surgical Safety Checklist. This was an initiative of the World Health Organization's (WHO) Safe Surgery Saves Lives Program. The mortality rate (at 30 days) decreased from 1.5 to 0.8% following implementation [86]. A global commitment by the sedation community to develop checklists to foster teamwork and the "safety culture" may ultimately improve patient outcome [84, 87].

Collecting Outcome Data to Guide Safety and Practice Parameters: Adoption of Standardized Definitions of Sedation-Related Adverse Events

As described previously, the works of the Pediatric Sedation Research Consortium and the ketamine individual patient data meta-analysis are important first steps toward generating the data required to carefully assess sedation practice in children outside the OR [1, 2, 75]. Recently, the World Society of Intravenous Anesthesia (World SIVA) established an International Sedation Task Force (ISTF) represented by 26 members from multispecialties, both adult and pediatric, from 11 countries. The ISTF has proposed an Adverse Event Reporting Tool designed to standardize the collection of sedation outcome data worldwide (Table 20.2) [88]. This tool is an open-access web-based tool, available to providers globally (www.AESedationReporting.com or www.InternationalSedationTaskForce.com). The data collected will be available to individual and institutional users and will, in addition, populate the global ISTF sedation database. The collection of large data from multi specialists globally will be an important first step to identify and carefully evaluate the range of variables which effect sedation-related adverse event rates. Such studies must be broad reaching in scope yet flexible enough to consider new developments in sedation techniques and monitoring as well as the use of the ever-emerging new sedation drugs that become available.

Only through rigorous adherence to the use of standardized adverse events definitions and reporting structures such as described in the Quebec Guidelines and by the ISTF, will standardized data sets be compiled allowing for the aggregation of data and meaningful comparisons of sedation studies to be made. National and international multispecialty collaboration will be required to develop databases with sufficient patient numbers and the clinical data required to develop and evaluate sedation practice based on patient populations and providers, procedures performed, and drugs administered. The feasibility of such a collaborative endeavor requires not only cooperation of multiple specialties using cutting-edge data collection technology but also a level of funding which to date has not been realized.

Sedatives: Exploring New Agents and Alternative Methods and Modes of Delivery

The ideal agent for procedural sedation would provide analgesia, anxiolysis, amnesia, and somnolence rapidly and predictably with no adverse effects. Ideally, this drug would be devoid of

respiratory side effects and ensure hemodynamic stability. To date, such a drug does not exist. It is highly unlikely that such a sedative will ever be developed. Thus, alternatives could include the introduction of sedatives which are reversible or new delivery methods. Fospropofol is a medication which was originally intended to be offered as a sedative that confers the same advantages of propofol (relatively rapid onset of sedation, brief time to recovery) with the added benefit of having less associated risk of respiratory depression [89–93]. It did not receive FDA approval as a sedative and instead has the same "anesthetic agent" labeling as propofol [89, 94]. Further studies are needed to determine the efficacy and safety profile of fospropofol, as currently the published studies are largely limited to adults undergoing gastrointestinal endoscopy procedures [90–92].

There does not appear to be any new sedatives in development. Perhaps then, it may be beneficial to explore alternate routes to deliver sedatives and analgesics which are currently already available. As different routes (intramuscular, sublingual, intranasal, buccal, rectal, oral, intravenous, subcutaneous) of delivery have different uptake and onset of action, perhaps their efficacy, outcome, and adverse event profile differ. The development of nonparenterally administered sedatives would offer alternatives to establishing intravenous access. This model already exists for some opiates. Fentanyl has been well described for transmucosal administration, but has not been developed for use in procedural sedation [95, 96]. Intramuscular ketamine has been well described in children and is currently a widely used option for those children who do not require intravenous access [20, 61, 97]. Nitrous oxide offers the advantages of an inhalational delivery method and has been used for procedural sedation for almost a century, especially in dentistry and oral surgery, and will likely continue to play a large role in the sedation of children [18, 19, 98]. Advances in nitrous oxide delivery systems may someday enable children to assist in the self-administration of nitrous oxide via a patient-controlled delivery system, which only delivers when triggered by inspiratory pressure, has a built-in scavenging system, and guarantees that a hypoxic mixture will never be delivered.

In addition to exploring outcomes with different routes of sedation, the future of sedation could rely on our ability to incorporate and validate new delivery methods. Targeted controlled infusions (TCI) are another option for more precise drug delivery. TCI infusion devices deliver a medication to a target blood concentration (brain) using validated pharamocokinetic models to achieve the targeted end point. TCI, as outlined in Chap. 23 (Absalom), is already being used worldwide by the anesthesia community as a method to titrate the intravenous anesthetic to the patient's physiological vital signs and predicted plasma serum levels [99–101]. Adult TCI models for many medications (ketamine, remifentanil, propofol, fentanyl) have been incorporated into specialized TCI infusion pumps which are widely used in Europe, but are not available in the United States (Alaris PK Syringe Pump, Cardinal Health, Switzerland; Master TCI, Fresenius Kabi, Germany; Perfusor Space, Braun, Germany). To date, no TCI infusion pump has been approved for use in the United States and no company has applied to the FDA for approval [27]. Advances in patient-controlled infusions or TCI, and more importantly, the development of pediatric models for TCI delivery may allow currently used sedatives, analgesics, and anesthetics to be administered to children in a more precise and safe manner.

Other delivery methods are also being explored. Currently, a computer-assisted personalized sedation device, CAPS, is being developed for adult usage. SEDASYS (Ethicon Endo-Surgery Inc., Cincinnati, OH) is a CAPS device that recently completed a multicenter Phase III trial delivering propofol for GI endoscopy [102]. CAPS is designed to integrate patient data into computerized programs in order to guide drug delivery. The goal of CAPS is to provide moderate sedation, with patients still able to respond to verbal or tactile instructions. Initial CAPS outcome data in adult patients undergoing gastrointestinal endoscopy appear promising [102, 103]. In June 2009, the FDA Advisory Committee for Anesthesiology and Respiratory Therapy Devices

recommended that the FDA approve the SEDASYS device, with a few caveats; the agency should require special training on the device for physicians and should require teams of at least three clinicians – including 1 doctor or nurse. The advisory committee also recommended that the system be limited to adults aged 70 or younger and that additional studies were needed. The FDA has subsequently turned down the request for Sedasys approval [104].

The future of pediatric sedation may well rest in the development and introduction of TCI and CAPS (for those children who are developmentally and cognitively able). A collaboration between the pharmaceutical and device industry as well as the clinical investigators will be essential not only to trial the CAPS, but also to create TCI models for children. The potential application of CAPS for pediatric use could offer cognitively able children the ability to control the delivery of their own sedation and analgesia. The future of CAPS and TCI for the pediatric population in the United States and abroad depends on pediatric trials, industry initiative, financial support, and the FDA's commitment to approach this new technique with an open mind.

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ERRATUM TO

The History of Sedation

Robert S. Holzman

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In the original version, the names on page 4 were incorrectly spelled in the following sentence: The most prominent of the Arab writers on medicine and pharmacy were Rhazes (865–925 CE) and Avicenna (930–1036 CE), whose main work was *A Canon on Medicine*.

The correct spelling is as follows:
The most prominent of the Arab writers on medicine and pharmacy were Al Razi (865-925 CE) and Ibn Sina (930-1036 CE), whose main work was *A Canon on Medicine*.

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