Pain Assessment and Management

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Introduction

The neonate shows unique responses to nociceptive inputs that are a result of immature sensory and motor systems. In addition, physical development and the maturation of drug metabolism and elimination pathways can profoundly impact the efficacy, toxicity, and side effects of analgesics. Important functional differences in pain processing mechanisms are present at the site of pain and in the CNS that lead to profound differences in pain signaling in the neonate compared with the adult. Immature and uncoordinated motor systems change and restrict the range of possible behavioral responses to pain, and postnatal changes in the expression, distribution, and function of transmitters and receptors involved in the actions of analgesics influence their effects. The neonatal period is characterized by profound neuroplasticity and it appears that as a consequence both painful events and exposure to certain compounds, notably some analgesics, have the potential to cause long-term adverse effects in this age group that would not occur at older ages. Therefore, the planning and implementation of safe and effective analgesia for neonates cannot simply be extrapolated from scaled-down versions of techniques used in older children and adults. Rather, they must be carefully constructed and implemented on the basis of a clear understanding of developmental neurobiology and pharmacology.

In this chapter, the development of nociception, the assessment of pain in the preterm and term infant and the principles of perioperative and procedure-related pain management will be discussed.

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The Development of Nociceptive Systems

The neonate is known to be relatively much more sensitive to nociceptive pain, i.e., potentially tissue-damaging or noxious sensory inputs than are older children and adults. Evidence indicates that premature infants from 24 weeks gestation manifest a full range of neurohumoral and metabolic responses to painful stimulation [1]. Whether the premature infant recognizes the nociception as pain as in adults and distinguishes it from other conditions remains unclear. Nociceptive thresholds are lower at birth but increase as a function of developmental age throughout infancy and childhood [2]. Studies of thresholds to mechanical stimuli (touch, pressure) in infants from preterm to 3 months of age show a clear linear relationship between the mechanical forces needed to trigger a reflex withdrawal response and chronological age [1, 3]. This increase in sensitivity is important; the physiological consequences of unmodified painful tissue-damaging inputs at this age were first clearly demonstrated in human studies that measured the "stress" response to major surgery in neonates who received "light" general anesthesia. The results included a massive, robust, and potentially harmful neuroendocrine stress response to pain, prevented by stronger anesthesia and analgesia, that occurred in neonates and infants at the youngest ages [4, 5]. In addition, pain relief during and after surgery improved important associated postoperative physiological outcomes such as respiratory function, highlighting the importance of analgesia in overall management strategies [5]. Many aspects of maturation are subject to activity-dependent developmental control. For example, there is concern that abnormal events during the neonatal period such as severe pain may alter normal development and lead to adverse long-term consequences to sensory processing mechanisms. In fact, surgery or injury in the neonatal period has been shown to change nociceptive thresholds and the response to subsequent pain months or even years later, although the precise mechanisms involved and the exact roles of pain intensity and analgesia are still not

J. Lerman (ed.), *Neonatal Anesthesia*, DOI 10.1007/978-1-4419-6041-2_14,

fully understood [6–8]. In order to fully appreciate the actual and potential consequences of pain in the neonate, it is necessary to understand how the infant processes nociceptive information and how these inputs are capable of altering CNS development.

Pain Processing Mechanisms

Nociceptors and sensory pathways are present from embryonic stages of development, but they undergo considerable postnatal reorganization and functional change. Refinement of sensory-motor coordination and the development of complex integrative central processing functions, particularly in the brain, take place throughout infancy, childhood, and adolescence although some of the most important, rapid and profound changes occur during the neonatal period.

CNS plasticity, or the capacity for change and adaptation in the central nervous system, is probably never greater than during this period. In fact, such plasticity is essential for neural development, and "normal" level of activity in nociceptive pathways is one mechanism by which this process is controlled. Conversely, unmodified abnormally high levels of activity such as during surgery without anesthesia or severe pain without analgesia may be contributors to some of the long-term changes in pain perception.

Basic Nociception

Neonates exhibit reduced response thresholds to touch, heat and pain that gradually increase as the nervous system matures. These changes are mediated by alterations in the central connections and function of nociceptors and activity in modulatory pathways; they are briefly summarized in Table 14.1. Painful mechanical, thermal, and chemical stimuli are normally detected by polymodal slow conducting C and fast A-delta fiber nociceptors, whose cell bodies are located in the dorsal root ganglion (DRG) and whose central terminals are mostly found in nociceptive specific areas of the superficial dorsal horn of the spinal cord (laminae I and II, Fig 14.1a). A-delta fibers terminate directly on ascending "projection" neurons in lamina I, whereas C-fibers generally terminate on interneurons located in lamina II. Fast-conducting A-beta fibers mostly detecting innocuous touch and pressure terminate in deeper laminae of the cord.

In early development, these central terminals are relatively less well localized, and those of low-threshold A-fibers overlap with C-fiber terminals in lamina II (Fig 14.1b), thereby potentially activating nociceptive projection neurons when stimulated. A reduction in specificity due to this structural difference is augmented by lack of myelination and immature ion channel kinetics that alter neuronal conduction times and synaptic strength leading to a more diffuse central response to peripheral stimuli. Intrinsic spinal cord and descending inhibitory controls are also less well organized and reduced in strength. In contrast to the adult, contralateral cutaneous inhibitory receptive fields are not matched to their corresponding excitatory fields [6]. Cutaneous receptive fields, the area of skin that excites an individual sensory neuron when stimulated, are relatively larger and more overlapping at birth such that each stimulus is cable of inducing a response in many more neurons at this time [9]. This lack of specificity, organization, and control is mirrored in motor circuits such that output responses are also more diffuse and less well integrated spatially and temporally [6]. Although little is currently known about nociceptive processing in higher centers of the brain, physiological studies in premature neonates have demonstrated that painful inputs are capable of producing measurable responses from at least 24 weeks postconception [10].

Sensitization, Inflammatory and Neuropathic Pain

The decrease in sensory thresholds that develop at the site of an injury is known as primary hyperalgesia; it is accompanied by a temporary reduction in thresholds both in the surrounding non-injured tissue and at distant sites known as secondary hyperalgesia. These post injury changes in sensitivity are characteristic of inflammatory pain, a normal part of the healing process. This pain responds fairly well to analgesics and will usually resolve spontaneously as the injury resolves. The processes responsible are known as sensitization, a phenomenon that involves many different mechanisms both in the periphery and CNS [11]. If damage occurs to nerves or nervous tissue, a state of more prolonged pain that is known as neuropathic pain may follow. Although neuropathic pain also

Table 14.1 Factors contributing to augmented pain responses in the neonate compared with the adult

Factor	Effect
Low-threshold A-fiber mechanoreceptors terminate centrally on nociceptive relay pathways	Weaker stimuli activate pain specific pathways
Weak intrinsic inhibitory mechanisms in spinal cord	Relative augmentation of pain signal
Reduced descending inhibition	Relative augmentation of pain signal
Large and overlapping cutaneous receptive fields	Amplification of stimulus effect due to increased numbers of neurons activated
Poorly localized and diffuse sensory-motor connexions	Less anatomically specific and more generalized motor responses

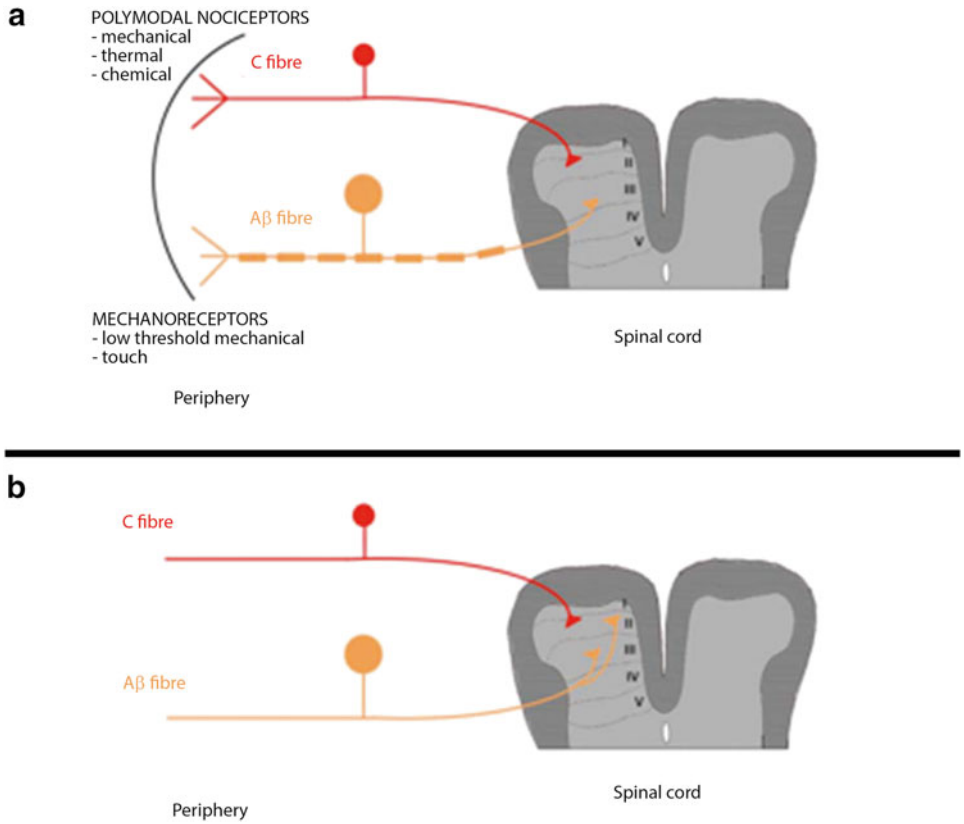

Fig 14.1 (**a**) Adult sensory inputs. (**b**) Neonatal sensory inputs

involves sensitization, unlike inflammatory pain, it often does not resolve spontaneously and is often difficult to treat. Neuropathic pain is a component of many chronically painful conditions such as phantom limb pain, diabetic neuropathy, trigeminal neuralgia, complex regional pain syndrome (CRPS) and many others. Both sensitization and the mechanisms underlying neuropathic pain are under intense research scrutiny with the aim of finding more effective analgesics [12].

These responses are different in neonates. Primary hyperalgesia at the site of an injury is known to occur from birth. Although recovery seems to be more rapid in neonates, a more prolonged inflammatory hyperalgesia has also been demonstrated after repetitive injury [13]. Secondary hyperalgesia appears to be less prominent at younger ages and is slower to develop [14]. Neuropathic pain has not been reported in neonates or infants, even after severe nerve injuries that represent a potent cause of pain in adults, such as brachial plexus damage [15]. Laboratory investigations have confirmed that nerve damage does not produce signs of neuropathic pain in either the neonatal or infant period. Recent studies have suggested that this may be due to immaturity of immune responses in the spinal cord involving microglia and peripheral cellular immunity known to maintain neuropathic pain in adults [16–18].

Long-Term Effects of Pain and Analgesia in the Neonatal Period

There is also evidence that pain in the neonatal period can lead to augmented responses to pain some time later. Boys who underwent neonatal circumcision without analgesia showed an enhanced response to pain at 3 months during immunization in comparison with those who did receive analgesia or were not circumcised [19]. Infants who had abdominal surgery repeated in the same dermatome as a previous operation before 3 months of age showed increased pain responses and analgesic requirements compared with controls [7]. Even more "minor" events such as heel stick blood sampling are a significant cause of pain in the neonate [20]. They too can lead to augmentation of the response to subsequent pain or may even be associated with more serious morbidity and poorer outcomes, especially when repeated frequently, e.g., in ICU [13, 21]. More complex and subtle effects have also been shown in cohorts of children who had neonatal surgery and ICU admission. A relative increase in temperature and touch thresholds near the site of surgery has been observed, but some children also have a more generalized decrease in temperature threshold [8, 22, 23]. Although the precise mechanisms behind these observations are not known, it is clear that sensory development depends on a

normal balance of sensory activity, and if this is disrupted, then abnormal patterns or even failure of normal maturation can occur. In the laboratory, maturation of nociceptive reflexes can be delayed or abolished by blocking sensory inputs with local anesthesia for long periods [24]. NMDA receptor activity has been shown to be important for normal sensory development in rat pups as chronic NMDA receptor blockade prevents the normal withdrawal of A-fibers from lamina II described above and a consequent persistence of low sensory thresholds [25].

A panoply of other physiologic sequelae have been reported after painful stimulation in premature infants. During the early brain growth period in premature infants, repetitive painful procedures have been shown to reduce both white matter and subcortical gray matter, leading to impaired brain development [26]. A growing body of evidence has associated repetitive painful procedures in the early postnatal period in premature infants with reduced weight gain and increased head circumference in the early postnatal period [27].

A number of drugs and chemical compounds may also cause long-term adverse effects when administered in the neonatal period over and above altered pharmacokinetic or pharmacodynamic responses due to immaturity. Neuroapoptosis, or programmed cell death, is a component of normal maturation in which cells that do not form functional connexions are eliminated. Drugs that are NMDA antagonists and/or GABA agonists in particular have the potential to markedly increase apoptosis to such an extent that neural development is damaged leading to deficits in, e.g., memory and learning. Although these effects have only been demonstrated in animal models to date, many general anesthetics have been implicated including ketamine (see below), a potent non specific NMDA antagonist that is also used as an analgesic.

These many factors impact the assessment, measurement and management of neonatal pain such that considerable specialist knowledge and skills are needed in order to deliver developmentally appropriate care.

Assessment of Pain

Frequent assessment of pain is an essential component of good pain management; however, this can be problematic in immature, preverbal infants. Accurate assessment including measurement of pain intensity contributes to the prevention or early recognition of pain, as well as for monitoring the effectiveness of analgesia [28]. Overall there are three fundamental approaches to pain assessment in children:

- Self-report: an individual's personal description of pain and rating of intensity
- Behavioral: observation of changes in facial expression and body posture due to pain
- Physiological: measurement of changes in physiological arousal consequent to pain

Obviously, self-report is impossible in neonates, and therefore one of the indirect measures of pain must be used. This is associated with disadvantages; perceived pain intensity is known to depend on many subjective influences apart from the degree of injury and tissue damage. Stress, anxiety, attention, and expectation, which are modulated by context, mood, previous experience, and underlying personality traits all contribute to the degree of unpleasantness of pain; the extent to which such factors can influence pain perception in the neonate is largely therefore a matter of speculation.

Nevertheless, in neonates, the observation of behaviors such as facial expression, cry, and posture and measurements of physiological variables such as heart rate and blood pressure have been used to assess pain and gauge its intensity in the absence of viable more objective alternatives. These observations and measures are subject to many external and internal influences aside from pain, which leads to difficulties in interpretation. For physiological variables in particular, a reduction in their reliability tends to occur over time due to homeostatic controls. In an attempt to improve accuracy, observations and measurements have been frequently incorporated into multidimensional pain measurement "tools" or "instruments" that are generally presented as checklists or scoring systems; the range of such observations and their validity and usability have been reviewed recently [29–32].

Pain Measurement Tools

A bewilderingly large number of pain assessment tools or scales have been designed for use in the neonate, some examples are given in Table 14.2 [1]. There is a considerable research literature on the subject, and it is now agreed that in order to be "fit for purpose", a pain assessment tool should have undergone a rigorous process of development.

To be considered reliable, an individual tool must be validated in the patient population and the clinical context and type of pain (e.g., postoperative or procedural) for which it is to be used. Despite the proliferation and availability of tools, they have not always adequately completed this process nor been used consistently or well; inconsistencies have been identified between reported assessment practice and documented practice [46–48]. Several factors may be responsible for this situation including the large number of scales that are available, limitations to individual scales that mean no single one can be universally recommended for use in all neonates in every situation, and "usability" factors that lead to individual user preferences that might not be scientifically appropriate.

Given the difficulty in finding the "Holy Grail" of behavioral pain scales for neonates, investigators have begun to pursue objective physiologic tools [1]. These pursuits have

Table 14.2 Pain measurement tools

BPS [33], behavioral pain score
CHIPPS [34], children and infants postoperative pain scale
COMFORT [35, 36]
CRIES [37]
CSS [38], clinical scoring system
DSVNI [39], distress scale for ventilated newborn infants
LIDS [40], Liverpool infant distress scale
NFCS [41], neonatal facial coding system
NIPS [42], neonatal infant pain scale
PAT [43], pain assessment tool
PIPP [44], premature infant pain profile
SUN [45], scale for use in newborns

included regional oxygen saturation in the brain (as in near-infrared spectroscopy), EEG, heart rate variability, skin conductance and neurohumoral responses. Although each appears to be an objective metric that may reflect the neonate's response to a painful stimulus, some of the metrics under investigation are invasive, others reflect a time course that may not correspond to the level of stimulation, and others remain imprecise. This remains an active work in progress that may require an aggregate of different measurements to provide a reliable and consistent metric of pain in the neonate.

Selecting an Appropriate Pain Assessment Tool

Recommendations and guidelines have been produced by a number of professional bodies outlining the currently available tools and advising on their suitability for different circumstances [29, 31, 32]. Training and support are required for successful implementation of the best validated tools, and this should be combined with ongoing monitoring and audits of practice. Three of the most widely endorsed tools are the PIPP [44], CRIES [37], and COMFORT [35] scales. The PIPP (Table 14.3) creates a score from 18 to 21 depending on gestational age and behavioral state, with 0–6 reflecting no pain, 6–12 reflecting mild to moderate pain and above 12 indicating severe pain; it is suitable for procedural pain and ongoing postoperative pain. CRIES includes similar indicators to PIPP: crying, oxygen requirements, increases in heart rate or blood pressure, facial expression and sleep behavior. CRIES creates a score from 0 to 10, similar to most self-report or observational measures of pain. The COMFORT [36] tool is more complex, originally developed in 1992 as an assessment of global comfort in pediatric intensive care. Since that time it has undergone a number of validation studies for both procedural and ongoing postoperative pain in intensive care. It is frequently chosen for use in the sickest neonates, e.g., after cardiac surgery.

Table 14.3 The PIPP [44] pain assessment tool

Gestational age	
≥36 weeks	0
32 weeks to 35 weeks 6 days	1
28 weeks to 31 weeks 6 days	2
<28 weeks	3
Behavioral state	
Active/awake eyes open facial movements	0
Quiet/awake eyes open no facial movements	1
Active/sleep eyes closed facial movements	2
Quiet/sleep eyes closed no facial movements	3
Heart rate maximum	
0–4 beats per minute increase	0
5–14 beats per minute increase	1
15–24 beats per minute increase	2
≥25 beats per minute increase	3
Oxygen saturation minimum	
0–2.4 % decrease	0
2.5–4.9 % decrease	1
5.0–7.4 % decrease	2
7.5 % decrease or more	3
Brow bulge	
None (≤9 % of time)	0
Minimum (10–39 % of time)	1
Moderate (40–69 % of time)	2
Maximum (>=70 % of time)	3
Eye squeeze	
None (≤ 9 % of time)	0
Minimum (10–39 % of time)	1
Moderate (40–69 % of time)	2
Maximum ≥70 % of time)	3
Nasolabial furrow	
None (≤9 % of time)	0
Minimum (10–39 % of time)	1
Moderate (40–69 % of time)	2
Maximum (≥70 % of time)	3
Score total (0–21)	

Planning and Organizing Pain Management

Multimodal or Balanced Analgesia

Current strategies for the treatment of acute pain are centered on the concept of multimodal analgesia, which was first proposed in order to increase the efficacy of analgesics while reducing their adverse effects [49]. The supporting rationale is that the major pharmacological groups of analgesics act on different components of pain pathways and as such their effects are likely to be complementary. This is also likely to be true in the neonate, but developmental factors influencing the effects and therefore appropriateness of many analgesics must also be considered. It is logical to use combinations of

analgesics, such as acetaminophen, opioids, and local anesthetics in conjunction in order to achieve the optimum effect while keeping the dose of each, and therefore side effects, at a moderate level. Sucrose and non-pharmacological pain management strategies such as nonnutritive sucking (NNS), swaddling, massage, etc. also have an important place in neonatal pain management, particularly for procedural pain, and should therefore be included in a multimodal regimen where it is appropriate.

Information and Protocols: Pain Management Plans

The provision of training and education for healthcare workers and availability of written and verbal information for families and carers are pivotal for successful pain management. Analgesic regimens should be pre-planned wherever possible and implemented with supporting educational programs, provision and maintenance of necessary equipment and clear developmentally appropriate management protocols. Pain management protocols must be sufficiently flexible to allow for differences in analgesic requirements due to developmental age and other factors; they should include a pain assessment and reassessment plan, encompass management of background and incident (breakthrough) pain and stipulate monitoring and management of adverse effects.

A well-designed protocol will therefore ensure efficacy and uniformity of treatment and facilitate ongoing evaluation of effectiveness. Protocols for pain management should also be designed in conjunction with ongoing global management strategies such as family-centered and developmental care [50, 51]. The implementation of family-centered care involves the establishment of a partnership between parents or carers and nursing staff and other healthcare workers that substantially increases parents' role in their child's in-hospital care. Developmental care in NICU is an increasingly popular strategy for reducing stress-related morbidity in premature neonates; stressful and painful inputs are reduced by observing responses on an individualised basis and carefully reorganizing and planning care [52].

Developmental Pharmacology of Analgesics

Relatively few analgesics have a clearly established role in neonatal pain management. Detailed analgesic clinical pharmacology is discussed in other chapters.

Acetaminophen (Paracetamol)

Acetaminophen is an antipyretic and mild analgesic that has been widely used for all ages, including premature neonates. Acetaminophen is used for the management of pain of mild to moderate severity; more severe pain is not controlled by acetaminophen alone. It is often combined with more potent analgesics for postoperative pain after major surgery in neonates, with conflicting results: one study showed significant morphine-sparing effect of intravenous paracetamol [53], whereas another showed no additional effect of rectal acetaminophen when combined with morphine [54].

The precise mechanism of action of acetaminophen is unknown, but central cyclooxygenase (COX) inhibition is probably important; other mechanisms have also been proposed including NMDA and serotonin antagonism and a possible action on cannabinoid receptors [55–57]. Alterations in the pharmacokinetic handling of acetaminophen have significant implications for safe dosing in neonates. Gastrointestinal absorption is delayed in premature neonates, whereas rectal bioavailability is initially greater in the premature and then decreases toward the usual value of 0.5 with increasing age [58]. The volume of distribution decreases and clearance increases from 28 weeks postconceptional age, resulting in a gradual decrease in the elimination half-life.

Acetaminophen is metabolized via both sulfation and glucuronidation, and the increased maturity of the sulfation pathway early in development and relatively high levels of glutathione at this time may provide some "protection" against toxicity in neonates [59]. However, as many kinetic studies have investigated single-dose administration only, caution is warranted with repeated dosing for more than two or three days [59]. Increased production of the reactive product N-acetyl-p-benzoquinoneimine occurs leading to liver toxicity if the usual metabolic enzyme systems become saturated due to overdose or if glutathione is depleted (e.g., with prolonged fasting).

Dose guidelines based on formulation, route of administration, weight and developmental age have been determined by pooled population analysis (Tables 14.4 and 14.5). Antipyretic plasma levels are 10–20 mg/l, levels required for analgesia are thought to be similar, and so most dosing regimens aim to maintain trough plasma concentrations of 10 mg/l [61]. A greater initial dose followed by maintenance doses not exceeding recommended maximum daily doses is generally recommended. Peak plasma levels are rapidly achieved after oral ingestion, but there is a 1–2 h lag before the maximum therapeutic effect; the onset of analgesia after IV administration may be much faster [62]. As rectal bioavailability is much reduced and more variable than oral bioavailability, greater initial doses are recommended when this route is used except in the premature infant. Two intravenous preparations of acetaminophen are available: IV acetaminophen and propacetamol. Propacetamol is a prodrug, which is hydrolyzed to 50 % acetaminophen and is therefore administered in twice the dose of the native drug, i.e., 1 g propacetamol is equivalent to 500 mg acetaminophen. This is a

Table 14.4 Acetaminophen dosing guide—oral and rectal administration

Age	Route	Loading dose	Maintenance dose	Interval	Maximum daily dose	Duration at maximum dose
28–32 weeks PCA	Oral	20 mg/kg	10–15 mg/kg	8–12 h	30 mg/kg	48 h
	Rectal	20 mg/kg	15 mg/kg	12 h		
32–52 weeks PCA	Oral	20 mg/kg	10–15 mg/kg	6–8 h	60 mg/kg	48 h
	Rectal	30 mg/kg	20 mg/kg	8 h		
>3 months	Oral	20 mg/kg	15 mg/kg	4 h	90 mg/kg	72 h
	Rectal	40 mg/kg	20 mg/kg	6 h		

PCA post-conceptual age

Table 14.5 Intravenous acetaminophen/propacetamol dosing guide[a]

Age	Drug	Loading dose (mg/kg)	Maintenance dose (mg/kg)	Dose interval	Maximum daily dose (mg/kg)
<32 weeks PCA	Propacetamol	40	20	12 h	60
	Acetaminophen	20	10	12 h	30
32–36 weeks PCA	Propacetamol	40	20	8 h	80
	Acetaminophen	20	10	8 h	40
36–52 weeks PCA	Propacetamol	40	20	6 h	100
	Acetaminophen	20	10	6 h	50
>1month	Propacetamol	30	30	6 h	120
	Acetaminophen	15	15	6 h	60

[a]Adapted from Allegaert et al. [60]

potential source of confusion and error [60]. The clearance of propacetamol is reduced in infants less than 1 year of age, thus reducing the maintenance doses [63]. Histamine release, pain on injection and contact dermatitis in healthcare workers have been reported with propacetamol. Additionally, mild platelet dysfunction has been reported [64, 65]. Intravenous acetaminophen appears to be devoid of these drawbacks, and therefore it has gained widespread acceptance in pediatric practice.

Several cases of massive overdose of IV paracetamol have been reported in preterm neonates and young infants to date [66–68]. In all instances, full recovery occurred without long-term sequelae. These did not appear to be the result of confusion of paracetamol with propacetamol. Recognizing the risk for potential liver failure or death from an iatrogenic overdose of acetaminophen in a neonate should prompt every institution to implement very tight controls on the dose of paracetamol when it is prescribed for neonates.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are not currently used in neonates for analgesia due to the uncertainty regarding their efficacy, and potential for adverse effects results in an unfavorable benefit-risk ratio. They act by inhibition of cyclooxygenase, enzymes that regulate many cellular functions by the production of prostaglandins and other substances. Prostaglandins have multiple roles in early development, and inhibition of their synthesis with NSAIDs may potentially result in the disruption of the sleep cycle, an increased risk of pulmonary hypertension, alterations in cerebral blood flow, decreased organ perfusion and renal function and disrupted thermoregulation [69].

In premature neonates in intensive care, prophylactic intravenous indomethacin reduces both the need for surgical ligation of patent ductus arteriosus and the incidence of grades 3 and 4 intraventricular hemorrhage. Reductions in cerebral, renal, and mesenteric blood flow velocity occur for 2 h after bolus indomethacin, but can be minimized by continuous infusion. Renal effects are also less with the use of ibuprofen compared with indomethacin. There is therefore a potential to reduce NSAID-related adverse effects. However, laboratory studies have shown a reduced efficacy of NSAIDs in young rodents, casting doubt on their value as analgesics in infants [70].

Opioids

Morphine is the prototypic opioid, having been extensively investigated in the neonate and used to treat severe acute pain after surgery and in the ICU. Dose requirements and clinical responses to opioid agents differ markedly between premature and term neonates and infants and children. Multiple factors contribute to these differences including age-dependent alteration in body composition and organ function influencing opioid pharmacokinetics and genetic and developmental factors that change opioid pharmacodynamics. Therefore, regular pain assessment with individual titration

and adjustment of doses according to response is required to achieve analgesia and minimize adverse effects. Tolerance leading to dose escalation and subsequent physical withdrawal response if opioid infusion rates are reduced too rapidly are distressingly frequent problems after medium- to long-term use in intensive care [71]. Other more lipophilic opioids such as hydromorphone, fentanyl, and remifentanil are also sometimes chosen for acute pain management in neonates and are therefore discussed below along with tramadol and the morphine prodrug, codeine.

Morphine

Morphine can be given orally or parenterally. Morphine solutions are generally well absorbed orally, but the pharmacokinetics and efficacy of oral opioids have not been clearly established in neonates. Oral morphine can be give at a dose of 0.2 mg/kg every 4 to 6 h in monitored non-ventilated neonates (Table 14.6). Parenteral morphine is usually given intravenously either by intermittent dosing, continuous infusion or in a nurse-controlled analgesia (NCA) regimen (Tables 14.5 and 14.6) [72]. Subcutaneous morphine is also used. The pharmacokinetics and clinical use of morphine in neonates have been reviewed extensively [73–76]. The pharmacokinetics of IV morphine are developmentally regulated. In the neonatal period, the pharmacokinetics are characterized by high inter-patient variability and reduced clearance, rendering the clinical effects of morphine less predictable than in older children. In neonates 1–7 days of age, the clearance of morphine is markedly diminished, being 30 % of that of older infants and children. As a result, the elimination half-life is approximately 1.7-fold greater than in older children [76, 77]. Infusion rates and dose intervals must therefore be adjusted according to both age and weight of the neonate, to avoid accumulation. Although the plasma levels associated with analgesia are not well defined, a mean steady-state plasma concentration of 10 ng ml^{-1} is a reasonable target in the neonate. This level may be achieved in children in intensive care after noncardiac surgery with a morphine hydrochloride infusion of 5 mcg h^{-1} kg^{-1} at birth (term neonates), 8.5 mcg h^{-1} kg^{-1} at 1 month, 13.5 mcg h^{-1} kg^{-1} at 3 months, 18 mcg h^{-1} kg^{-1} at 1 year and 16 mcg h^{-1} kg^{-1} for 1- to 3-years-old children [75]. A recent retrospective audit of morphine consumption over a wide age range by the same investigators indicated that morphine infusion rates of 10 mcg h^{-1} kg^{-1} appear appropriate for neonates and infants 1–6 months of age, but given the interindividual variability in responses, the rate should be adjusted to the infant's pain level, concomitant medications, and physiological responses [78]. Conversely, a common threshold for respiratory depression in neonates, infants, and children has been defined as 20 ng ml^{-1} [79]. Any differences in efficacy observed between continuous infusion and intermittent boluses of morphine probably relate more to the age appropriate total dose of drug received, rather than the route of administration [80, 81] Sedation and respiratory depression are the most frequently reported adverse events after morphine (and other opioids) [82] administration. Adverse effects of morphine can be reversed by administering the opioid antagonist naloxone A timely administration of naloxone should facilitate complete recovery from the adverse effects.

Table 14.6 Morphine dosing and morphine infusion

Morphine dosing	
Preparation	
Oral solution	200 mcg/kg, 4–6 hourly
Intravenous	25–50 mcg/kg initial dose (titrated according to response)
	25 mcg/kg every 30 min–1h
Morphine infusion	
Preparation	Morphine sulfate 1 mg/kg in 50 ml solution
Concentration	20 mcg/kg/ml (0.02 mg/kg/ml)
Initial dose	0.5–2.5 ml (0.01–0.05 mg/kg)
Infusion rate	0.1–0.6 ml/h (2–12mcg/kg/h)

Box 1 Nurse-Controlled Analgesia (NCA)

NCA is a demand-led alternative for patients who are too young or unable to use PCA (patient-controlled analgesia). It is designed to provide safe, potent, flexible and convenient pain control by combining the possibility of a continuous opioid analgesic infusion with on-demand bolus doses of analgesia administered according to predetermined limits. NCA was first developed for infants and those children and adults who were unable to operate the PCA handset and was subsequently adapted for neonates [72]. The protocol for the initial infusion of NCA in a postsurgical neonate is shown in Table 14.7.

Table 14.7 NCA (morphine) protocol for neonates and infants

NCA[a] for neonatal use	
Preparation	Morphine sulfate 1 mg/kg in 50 ml solution
Concentration	0.02 mg/kg/ml
Initial dose	0.5–2.5 ml (0.01–0.05 mg/kg)
Pump programming	
Background infusion	0–0.5 ml (0–0.01 mg/kg/h)
NCA dose	0.5–1.0 ml (0.01–0.02 mg/kg)
Lockout interval	20 or 30 min

[a]NCA is a demand-led, flexible morphine infusion system using a PCA infusion pump [72]. It is suitable for neonates not receiving respiratory support provided they are closely monitored by appropriately trained staff

Fentanyl

Fentanyl is a synthetic, high-potency (100x morphine) lipid-soluble opioid; its main use is for intraoperative analgesia where its rapid onset, short initial half-life, and cardiovascular stability at larger doses are an advantage. Fentanyl is also used by infusion in ICU, and it has some advantages for procedural pain owing to its rapid onset. Unfortunately it also creates the potential to more rapidly develop tolerance after prolonged use and may cause opioid withdrawal syndromes.

After a single intravenous dose, the duration of action of fentanyl is 30–45 min. Given its high lipid solubility, the pharmacokinetic profile of fentanyl is context sensitive, such that its half-life progressively increases with the duration of the infusion [83]. High-dose fentanyl has been associated with chest wall rigidity and subsequent difficulty in ventilation. Accordingly, large doses are usually given only when respiration is controlled [84]. Fentanyl can also be given neuraxially; in the epidural space, it is used alone or in combination with an infusion of local anesthetic after major surgery [85, 86]. Alfentanil and sufentanil are fentanyl analogs with different potencies and durations of effect. Their principal use is during anesthesia, but they have also been used for postoperative pain and pain due to brief procedures particularly in the ICU [87, 88]. Sufentanil is more potent, but otherwise very similar to fentanyl in its clinical effect. It has been administered by infusion in the ICU, but probably does not offer significant advantage. Alfentanil is less potent than fentanyl. Its pharmacokinetics have been studied in the neonate. Its duration of action after a single dose is relatively brief, making it suitable for use during tracheal intubation [78]. However like fentanyl, doses effective for painful procedures can lead to chest wall rigidity in neonates and therefore should probably only be used if ventilation is controlled [89].

Remifentanil

Remifentanil is an ultrashort-acting fentanyl analog that is metabolized by the ubiquitous tissue and plasma esterases. Consequently, its elimination is rapid and fixed and independent of liver and renal function. The context sensitive half-life of remifentanil remains in the order of a few minutes even after several hours of infusion, a product of its rapid degradation by esterases. This characteristic has obvious advantages in anesthesia and sedation practice. Indeed, the role of remifentanil in pediatric anesthesia and intensive care has been reviewed recently [90].

Although remifentanil has been used during surgery and in ventilated neonates in ICU, the rapid development of tolerance and possibility of opioid-induced hyperalgesia are potential problems. If remifentanil is used during anesthesia, then longer acting opioids are usually introduced immediately before or after awakening to prevent severe pain from developing in the early postoperative period [91].

Hydromorphone

Hydromorphone is a potent semisynthetic morphine derivative that is popular in pediatric practice having been used extensively in PCA and epidural analgesia regimens in older children. Hydromorphone is approximately 4 or 5 times more potent than morphine and has a lipid solubility intermediate between morphine and fentanyl. It has no active metabolites which is potentially an advantage in the neonates, although it has not been well described or studied in this age group.

Codeine

Codeine is a low-potency opioid that has been popular in pediatric practice. Its primary indication is for mild to moderately severe pain. Traditionally codeine has been chosen where respiratory depression, sedation, or other opioid-related side effects are a particular concern, e.g., in the neonate and after neurosurgery, although the use of codeine for these indications has been challenged because of uncertainties regarding its efficacy and safety [92].

Codeine is a morphine prodrug; about 10–15 % of each dose of codeine is metabolized to morphine by the cytochrome P450 enzyme CYP2D6, and this metabolite is thought to be responsible for its analgesic effect as analgesia cannot be demonstrated in human volunteers in whom the pathway is pharmacologically blocked. CYP2D6 activity is genetically regulated, with 5–40 % of individuals in some populations having reduced, little, or no activity ("slow and intermediate metabolizers"), and consequently is less able to produce morphine from codeine. This has led to widespread unpredictability in its analgesic effects [93]. Conversely "ultrarapid metabolizers" may experience adverse effects in the form of respiratory depression from the rapid conversion of codeine to morphine [92]. CYP2D6 activity is also developmentally regulated, with reduced activity in the very young [94]. Codeine should be avoided when pain assessment is difficult or impossible and in individuals with known polymorphisms of CYP2D6. In general, we do not recommend codeine for the management of pain in neonates.

Tramadol

Tramadol is a synthetic opioid analgesic that also inhibits serotonin and norepinephrine reuptake [95]. Its clinical pharmacology has been reviewed recently. It is used widely for acute and chronic pain in children, and there is an extensive body of literature describing its efficacy and indications. The pharmacokinetics of tramadol in neonates and infants have been investigated. Clearance is reduced in the neonate, but reaches 80 % of adult values by 1 month of age [96, 97].

No relationship has been established between postmenstrual age and O-desmethyltramadol production (see below).

As in the case of codeine, tramadol is metabolized by the cytochrome enzyme CYP2D6 to its major active metabolite

O-desmethyltramadol, which has a 200× greater affinity for the mu opioid receptor than the parent compound. CYP2D6 is genetically and developmentally regulated (see codeine metabolism above), which may hold implications for its use in very young patients. The effect of CYP2D6 polymorphism on the efficacy and disposition of tramadol at this time is unknown.

Opioid side effects have been reported to be less prominent with tramadol in neonates, although this has not been confirmed when equi analgesic doses were used [95, 98].

Novel Non-opioid Analgesics

Clonidine and Dexmedetomidine

Clonidine and dexmedetomidine are alpha$_2$ adrenergic agonists capable of producing analgesia both systemically and neuraxially. Clonidine has been more widely used and studied than dexmedetomidine to date. Clonidine has analgesic, sedative and antiemetic properties; it can also cause hypotension and bradycardia. It has been used as a sedative infusion in ICU areas and for the symptomatic treatment of effects due to the rapid withdrawal from opioids [99].

Pharmacokinetic data regarding alpha$_2$ agonists in neonates do not exist and in children are limited. After systemic administration, plasma concentrations of clonidine within the range 0.2–2.0 ng/ml are thought to be clinically effective [100]. The pharmacokinetics of epidural clonidine in 1–9-year-olds was similar to that in adults [101]. Dose-dependent sedation, hypotension, and bradycardia occur after systemic clonidine. Neonates appear to be more susceptible to both the effects and side effects of clonidine. Since the reporting of a case of severe delayed respiratory depression in a neonate who was given 2 mcg/kg caudal epidural clonidine, a number of similar reports have appeared in the literature that have resulted in an advisory to use caution when considering the use of clonidine by any route in this age group [102–105]. Epidural dexmedetomidine analgesia was also found to be developmentally regulated and relatively greater in neonates in a laboratory model. These data suggest that dexmedetomidine may be better tolerated than clonidine in neonates [106].

Ketamine

Ketamine is a glutamate NMDA receptor antagonist that has been used for many years as an intravenous general anesthetic. Its principal advantages include profound analgesia, relative preservation of respiration and respiratory reflexes and cardiovascular stimulation. Ketamine produces a state of "dissociative" anesthesia that has the disadvantage that emergence phenomena may occur including hallucinations and unpleasant dreams. After small doses (<1 mg/kg), ketamine is an effective analgesic. In particular, it reduces the hypersensitivity due to central sensitization after injury or surgery in both inflammatory and neuropathic conditions. Although there are numerous publications concerning the analgesic effects of ketamine, a recent systematic review concluded that its role in the management of postoperative pain in the adult remains unclear [107].

The NMDA receptor undergoes developmental changes in distribution, structure, and function. It is thought to play an important role in regulating neuronal plasticity during the developmental period [108]. The precise impact of these changes on the efficacy or toxicity of ketamine (or other NMDA antagonists) during the neonatal period remains incompletely understood. The principal uses of ketamine in neonatal practice have been as an intravenous induction agent in high-risk patients with cardiovascular disease and for procedural sedation. The potential for neurotoxicity from systemically or spinally administered NMDA antagonists is also a concern and has been the subject of considerable and ongoing debate [109]. Systemically administered ketamine, and a number of other substances including some sedatives and anesthetic agents, can produce damaging neurodegeneration in the rodent brain if exposure occurs during a critical period of early postnatal development [110]. The significance of these findings in humans and implications for clinical practice remain unknown at this time [111]. Early studies in primates indicate that similar histological damage is possible, but critically depends on the age at exposure, drug dose and duration of treatment, with the greatest risks being conferred inter-utero and in the first few days of life [112]. Spinally (epidural) administered preservative-free ketamine has not been clinically implicated in causing neurotoxicity, although recent research in rodents has led to the conclusion that the benefit-risk ratio is unlikely to be favorable in neonates and young children, and so it should be avoided [102, 113].

Local Anesthetics

Local anesthesia (LA) is very important in infant acute pain management, particularly during and after surgery and for procedural pain where opioid requirements and opioid-induced side effects such as depression of respiration can be reduced or avoided. Topical LA, LA infiltration, and peripheral and central regional analgesia are all used extensively to prevent or treat acute pain in neonates. The detailed pharmacology of local anesthetics is discussed elsewhere.

Lidocaine, Bupivacaine, Levobupivacaine and Ropivacaine

The amide-type LAs lidocaine and bupivacaine have been the most commonly used in neonates for several decades, and there is considerable clinical experience of their efficacy and safety at all ages. Lidocaine has a rapid onset and is of short to intermediate duration; it is used for local infiltration and regional nerve blocks, particularly where a rapid response is

required. EMLA (eutectic mixture of local anesthetics) is a combination of lidocaine and prilocaine for topical analgesia—see below for a detailed description. Bupivacaine has a slower onset and long duration, 4 h analgesia or longer can be expected after single-dose central nerve blocks, and consequently it has been the first choice for postoperative analgesia. Their pharmacology and pharmacokinetics have been well investigated and were reviewed recently [114]. Bupivacaine is a racemic mixture. The S(+) enantiomer, levobupivacaine, has a slightly improved in vivo and in vitro safety profile compared with bupivacaine, but is otherwise similar [115, 116]. Ropivacaine is also a levo-enantiomer amide LA with similar clinical properties to bupivacaine except that motor block is slower in onset, less intense and shorter in duration [102]. Ropivacaine may have theoretical advantages during prolonged infusion in neonates and infants, when compared with bupivacaine, as the former's context sensitive half-life does not increase with the duration of infusion [102].

Toxicity of LAs depends on the age of the patient, the drug, absolute dose, and route of administration. Neurotoxicity and cardiotoxicity have been reported in neonates who may have a reduced threshold for toxicity, although toxic events are quite rare provided dosage recommendations are followed [117]. LAs are extensively protein bound (>90 %), with the free, unbound fraction being the pharmacologically active fraction. AAG (alpha-acid glycoprotein) and albumin are the most important plasma proteins that bind drug; AAG levels in blood are reduced in the neonate resulting in increased unbound fractions of lidocaine and bupivacaine [118, 119]. Plasma bupivacaine concentrations >3mcg/ml are associated with neurotoxicity in the awake adult, cardiotoxicity with levels >4mcg/ml. Equivalent blood concentrations in neonates are not known, but toxicity has been reported after epidural bupivacaine infusion at doses greater than 0.3 mg/kg/h, leading to a reduction in the recommended infusion rate in neonates to 0.2 mg/kg/h or less [120, 121] and duration of infusion of 48 h [122]. In contrast to levels after epidural bupivacaine, the plasma levels after epidural ropivacaine infusion in infants <1 year of age did not continue to increase with the duration of the infusion, although the absolute levels and free fraction were similarly increased at younger ages [123].

EMLA, Amethocaine Gel, and Other Topical LA Preparations

Topical local anesthesia has revolutionized the practice of minor needle-related procedures such as venipuncture, venous cannulation and lumbar puncture [124]. A number of preparations are available, the most frequently studied and used being EMLA and Ametop (amethocaine or tetracaine gel).

EMLA is a eutectic mixture of lidocaine and prilocaine such that the combination has a melting point that is less than either of the constituents. This mixture, formulated as a cream, effects local anesthesia when applied to intact skin for approximately 60 min under an occlusive dressing, with a duration of analgesia that may last several hours. If applied to the mucosa, however, the absorption of the local anesthetic is much more rapid and extensive and may cause methemoglobinemia and seizures [125]. EMLA is suitable for use in the neonate in single doses; multiple doses should be limited to a maximum of 4 applications per day and under close supervision to avoid methemoglobinemia. Measurement of blood methemoglobin levels has been advised if multiple applications or large doses of EMLA are applied [126, 127]. Prilocaine causes methemoglobinemia indirectly via its primary metabolite, o-toluidine. Methemoglobin is an oxidized form of hemoglobin that has a reduced oxygen-carrying capacity. Methemoglobin reductase, the enzyme that catalyzes reduction to hemoglobin, is also developmentally regulated, rendering neonates susceptible to methemoglobinemia because fetal hemoglobin is more easily oxidized [128]. Minor side effects of transient paleness, or redness, and edema of the skin may occur after the application of EMLA.

Tetracaine, the essential ingredient in Ametop, is a potent ester-type local anesthetic. Given its systemic toxicity, its clinical use is limited to intrathecal and surface anesthesia. Four percent tetracaine gel (Ametop) produces surface anesthesia in about 30 min and has an absorption and elimination half-life of about 75 min and a duration of analgesia of 4–6 h. Only 15 % of topically applied tetracaine is bioavailable. Tetracaine produces a more rapid onset and longer lasting duration of effect than EMLA. It has been shown to be effective in the neonate [129, 130], although it may not be effective for all procedures [131]. Mild erythema at the site of application is frequently observed but of little consequence; edema of the skin, itching, and even blistering have been reported in older children but are rare in the neonate.

Sucrose

Sucrose solutions reduce physiological and behavioral signs of pain in neonates during brief painful procedures such as heel lance blood sampling [132]. This effect may be mediated by activation of descending modulatory pathways by activation of intrinsic opioid systems in response to the sweet taste [133]. The prescription for sucrose analgesia is 0.5–2.0 ml of a 24 % solution of sucrose administered 1–2 min before the painful stimulus [134]. Although studies have found that dosing ranges between 0.05 and 2.0 ml of 12–24 % solutions are effective [135], it can also be given using a pacifier or dripped directly onto the tongue using a syringe. The number of drops that should be used should be gauged by the infant's response to pain. However, there is no actual known analgesic dose. Coughing, choking, gagging and transient oxygen desaturation can occur. The safety of

multiple administrations in very small preterm infants has been questioned as changes in neurobehavioral responses were observed after repeated sucrose administration in this age group [136, 137].

Postoperative Pain Management

Postoperative pain management should always be planned before undertaking surgery [138]. Initiation of postoperative pain relief is usually considered to be part of the plan of anesthesia; patients should not normally be discharged from the PACU (postanesthesia recovery unit) or returned to the ICU until they are comfortable and an ongoing pain management plan is established. Pain management protocols should include pain assessment, monitoring, criteria for additional analgesia, management of side effects, and criteria for transition to simpler, usually oral, analgesia when appropriate. The range of surgical complexity and thus the range of postoperative pain in neonatal surgery cover the spectrum from relatively minor, as in the case of circumcision or uncomplicated inguinal hernia repair on otherwise well neonates, to major interventions in life-threatening circumstances carried out on very sick infants. Appropriate analgesia depends on the exact prevailing circumstances that would depend on the type of surgery, physical state of the child and available facilities for postoperative care and level of staff training. Some of the more commonly encountered procedures, divided into three groups of increasing complexity, are given in Table 14.8. Conventionally, analgesia is commenced intraoperatively as part of the plan of anesthesia using combinations of local anesthetics, opioids, and acetaminophen and suitable ongoing analgesia administered orally, rectally or parenterally as indicated.

Table 14.8 Common surgical procedures

Neonatal surgery
Group 1
Inguinal hernia repair
Pyloromyotomy
Orchidopexy, orchidectomy
Group 2
Duodenal atresia
Intestinal malrotation
Colostomy formation
Urogenital malformations
Group 3
Bowel resections NEC
Esophageal atresia
Congenital diaphragmatic hernia
PDA repair
Congenital heart surgery

Group 1: Inguinal Hernia Repair, Circumcision, Pyloromyotomy, etc

Neonates presenting for this type of surgery are usually healthy; the procedures are relatively brief and are sometimes performed using minimally invasive laparoscopic techniques:

(a) Local anesthesia: Caudal epidural analgesia or simple local anesthetic nerve blocks such as ilioinguinal block and penile block are often effective. If these techniques are not suitable, then subcutaneous infiltration at the surgical incision or laparoscope port sites with a relatively long-acting local anesthetic such as levobupivacaine is an option.

(b) Opioid analgesia: Fentanyl or other suitable opioid administered as part of anesthesia can be continued into the postoperative period if necessary using oral morphine solution as oral intake is usually rapidly resumed. Oral morphine can be given every 4 h if necessary, but it is unusual for neonates to require more than one or two doses after these procedures.

(c) Acetaminophen: A loading dose should be administered during surgery, preferably intravenously. Oral and rectal dosing are options; the first dose can be given before surgery, but rectal absorption is less predictable in neonates. Acetaminophen can be continued orally at appropriate doses for 2 or 3 days as necessary.

Group 2: Major Gastrointestinal or Genitourinary Surgery

Although surgery can be quite prolonged and relatively invasive, the majority of neonates presenting for these procedures are healthy and can be expected to recover rapidly. A potential problem is that large doses of intraoperative opioids may be required to obtund physiological responses to surgery, which may result in delayed recovery and possibly necessitating postoperative respiratory support:

(a) Local anesthesia: Continuous epidural analgesia should be considered for this group as it allows early postoperative extubation and reduces the need for ongoing respiratory support.

(b) Opioid: High-potency analgesics such as parenteral opioids or local anesthetic infusions may be needed as part of a "balanced analgesia" approach. Intravenous opioid infusion may be needed postoperatively, and NCA (see above) should be considered because it is easier to adapt dose requirements to individual patients and circumstances.

(c) Acetaminophen: Intravenous paracetamol has been shown to reduce the postoperative morphine requirements in neonates and infants after major abdominal and

thoracic surgery [53]. Rectal acetaminophen failed to reduce morphine requirements in neonates after major abdominal surgery [54]. But as rectal absorption is unreliable and pain assessment difficult in these infants, further study is indicated before this strategy is abandoned. Acetaminophen, and particularly intravenous acetaminophen, should not be given at full dose for more than a few days because of potential toxicity. Therefore it may be prudent to delay its use until epidural or IV opioid infusions are being withdrawn on postoperative days 2 and 3.

Group 3: Cardiothoracic Surgery or Complex Gastrointestinal/Genitourinary Surgery

These infants are frequently unwell, in poor clinical condition or critically ill. Sepsis, cardiorespiratory insufficiency and significant blood loss can complicate the perioperative period. Few of these neonates are extubated within the first postoperative day. Premature neonates with necrotizing enterocolitis who need GI surgery or ventilator-dependent neonates with PDA are often too immature or too unwell to tolerate procedures such as epidural placement unless strongly indicated. Potent intravenous opioid analgesia by continuous infusion or NCA with or without acetaminophen is the mainstay of analgesia in this group. Postoperative pain management after cardiac surgery in neonates has been reviewed recently [139].

Analgesia for Neonates in ICU

Neonates who have undergone surgery require analgesia; this is usually given in the form of opioid infusions in ICU settings. Premature and other neonates in ICU who need respiratory support may also require pain relief, but there is ongoing and currently unresolved debate regarding whether the use of opioid infusions in neonates who are ventilated in ICU should be routine. Typically these infants undergo numerous painful medical procedures such as heel lance blood sampling, insertion of arterial lines, lumbar puncture and many others. Sedation and analgesia are often provided for laryngoscopy and insertion of the tracheal tube in the neonate, although maintaining the tube in the trachea may itself be painful. Aside from humanitarian and ethical reasons for giving analgesia, routine use of morphine infusions may improve cardiorespiratory stability in ventilated neonates. A pilot study has also suggested that the use of opioids may improve neurological outcome [140]. This benefit was not confirmed in a subsequent large study, which initially reported an association between bolus morphine administration and worse outcome [141]. Subsequent reanalysis of the data has revealed that poor neurological outcomes were related to pre existing hypotension and that morphine therapy was not a contributory factor [142]. However, morphine infusions can produce hypotension, and the safety, efficacy, and long-term outcomes of analgesia and sedation in ventilated neonates require further evaluation. Although evidence suggested that the use of morphine in neonatal animals confers possible long-term neurocognitive, neurobehavioral and neuroanatomical changes, two recent studies of ventilated premature neonates who were randomized to receive either morphine (10 μg/kg/h) or no morphine in the early postnatal period failed to show any serious long-term neurocognitive or neurobehavioral consequences in the morphine-treated group after 5 and then 8–9 years [143]. In contrast, midazolam, a sedative frequently used in older patients in intensive care, has been strongly associated with an increased incidence of poor neurological outcome in neonates [140]. Hence, the use of such drugs requires a careful benefit to risk analysis. Although there is currently insufficient evidence to support routine opioid infusions in ventilated neonates, morphine appears safer than midazolam as a sedative in this age group. As the risks involved are often subtle, difficult to measure, and their mechanisms poorly understood, the selective use of opioids based on the assessment of pain, clinical judgment, and the current best available evidence has been recommended [144, 145].

Procedural Pain

A number of documents including reviews, guidelines and policy statements have been published recently on the subject of procedural pain management in the neonate [146–148]. Analgesia for neonatal procedural pain has been relatively well studied, yet it is clear that many procedures are often poorly managed [20]. Painful procedures include blood sampling, insertion of intravenous and intra-arterial catheters, retinal laser treatment, insertion and removal of chest tubes, and tracheal intubation, among others. In some cases, procedures are performed on neonates that would always entail general anesthesia in older children and adults. This is not consistent with evidence that the neonate has increased sensitivity to nociceptive pain (see above). General considerations regarding procedural pain management are given in Table 14.9. Procedural pain management should include both pharmacological and non-pharmacological strategies whenever possible. For example, if feasible, breast-feeding mothers should be encouraged to breast-feed during the procedure [149–151]. Nonnutritive sucking, sucrose, or other sweet solutions are effective in term and premature infants, and tactile stimulation or kangaroo care (skin to skin contact) are

Table 14.9 Procedural pain management[a]

1. Consider if the planned procedure is necessary and how the information it will provide might influence care
2. Are available analgesics and pain management strategies likely to provide adequate pain relief? Is sedation or general anesthesia indicated?
3. Avoid multiple procedures if possible. Cohorting several procedures may be less stressful as long as effective analgesia is provided
4. Consider if the modification of the procedure (e.g., venipuncture is less painful than heel lance) would reduce pain
5. Allow sufficient time for analgesic drugs and other analgesic measures to be effective
6. Ensure that appropriate personnel are available, and enlist experienced help when necessary
7. Formulate a clear plan of action should the procedure fail or pain become unmanageable using the techniques selected

[a] Adapted from [138]. A guideline from the Association of Paediatric Anaesthetists of Great Britain and Ireland

useful strategies for brief procedures in the premature infant [152–154]. Published guidelines have reviewed the evidence for the effectiveness of pharmacological treatments for specific procedures, e.g., local anesthesia or opioids, and they should be consulted to inform locally developed protocols [147, 148, 154].

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