Sedation and Analgesia in Neurointensive Care

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Abstract

In the neurointensive care setting, specific considerations of sedation are required; sedation may act as a therapeutic agent itself, when causing a reduction in cerebral metabolic rate of oxygen, cerebral blood flow, and intracranial pressure and in the incidence of seizures. However, the physician must be aware of the effects of every sedative agent on cerebral physiology, in order to obtain beneficial effects and avoid side effects. In this chapter, the effects of sedative agents on cerebral physiology are described in order to provide knowledge for an adequate sedative strategy.

Keywords

Sedation • Cerebral metabolic rate of oxygen • Cerebral blood flow • Intracranial pressure • Seizures • Propofol • Benzodiazepines • Delirium

Introduction

Sedation and analgesia (S&A) are fundamental in the management of the critically ill patient. Recent emphasis on weaning from the ventilator and reducing ventilator-associated pneumonia has produced improved S&A guidelines that assure comfort, has reduced time on the ventilator, has resulted in a decreased intensive care unit (ICU) length of stay (LOS), and has prevented neurologic deterioration [1, 2].

The neurointensive care unit (NICU), when compared to the general ICU, requires special considerations. S&A used in the general ICU limits the stress response to critical illness, provides anxiolysis, improves patient–ventilator synchrony, and facilitates care. However, when used in the NICU, S&A is fundamental as a therapeutic strategy. For example, extracted data from the published reports of two large, randomized, pharmacologic, clinical trials on traumatic brain injury show the use of S&A in more than 90 % of the patients [3]. Nevertheless, clinical practice varies

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widely as a result of institutional and national biases and because individual patient's response to S&A differs from patient to patient and from time to time [4, 5].

Table 14.1 shows the ideal properties of a sedative drug for the NICU. Pharmacokinetic and cost characteristics of common sedative and analgesics used in the NICU are reviewed in Table 14.2. Neurophysiology characteristics of common sedative and analgesics used in the NICU are reviewed in Table 14.3 [6].

The literature available on the use of S&A in the ICU includes a recent summary published by the American Society of Critical Care Medicine [7], and analyzed in detail [8–11], it does not specifically address the use of sedatives in the NICU. Specific logistics include intracranial pressure control, reduction of cerebral oxygen consumption, and seizure reduction, which are the focus of this chapter.

Table 14.1 Properties of an ideal agent for neurointensive care sedation

Rapid onset and rapid recovery, allowing prompt neurologic evaluation
Predictable clearance independent of end-organ function, avoiding the problem of drug accumulation
Easily titration to achieve adequate levels of sedation
Reduced intracranial pressure by cerebral blood volume reduction or cerebral vasoconstriction
Reduced cerebral blood flow and cerebral metabolic rate of oxygen consumption, maintaining their coupling
Maintenance of cerebral autoregulation and normal cerebral vascular reactivity to changes in arterial carbon dioxide tension
Minimal cardiovascular depressant effects
Inexpensive

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Specific Rationale for the Use of Sedation and Analgesia in the Neurointensive ICU

Reduction of Cerebral Metabolic Rate of Oxygen Consumption

To maintain adequate oxygen availability and energy balance at the neuronal level, treatment is directed at both increasing oxygen delivery by optimizing cerebral and systemic hemodynamics and reducing cerebral metabolic demand [12–19]. Selected sedatives used in NICU offer a protective effect by reducing oxygen demand and increasing oxygen delivery [20–22].

The γ-aminobutyric acid (GABA) type A receptor system, the main fast-acting inhibitory neurotransmitter system in the brain, is the pharmacological target for many drugs used clinically to treat, for example, anxiety disorders and epilepsy, and to induce and maintain sedation titrated to the desired effect. GABA type A receptor stimulation results in a reduction of cerebral metabolism of O_2 ($CMRO_2$). For example, in healthy

Table 14.2 Pharmacokinetic parameters, dosing, and cost of sedative and analgesic agents presented in the text

	Intravenous bolus dose	Continuous intravenous infusion	Elimination half-time, h	Clearance, ml/min/kg	Metabolic pathway	Active metabolites	Cost
Lorazepam	0.02–0.06 mg/kg	0.01–0.10 mg/kg/h	10–20	0.75–1.00	Glucuronidation	None	Inexpensive
Midazolam	0.02–0.08 mg/kg	0.04–0.30 mg/kg/h	2.0–2.5	4–8	CYP3A4	Yes	Moderate
Fentanyl	25–125 μg	10–100 μg/h	3.7	13	CYP3A4	None	Inexpensive
Remifentanil	Not recommended	0.05–0.25 μg/kg/min	0.3	44	Plasma esterases	None	Expensive
Propofal	Not recommended	5–200 μg/kg/min	7.2	24	Hepatic	None	Expensive
Dexmedetomidine	1 μg/kg	0.2–0.7 μg/kg/h	2	8.2	Glucuronidation and CYP2D6	None	Expensive

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Table 14.3 Cerebral and systemic characteristics of the available molecules

	Propofol	Midazolam	Lorazepam	Fentanyl	Remifentanil
Rapid onset	+++	+++	+	+++	+++
Fast recovery	+++	++	+	++	+++
Easily titrated	+++	++	+	++	+++
ICP reduction	↓↓	↓	↓	↓/↔	↓/↔
CBF reduction	↓↓	↓↓	↓	↔	↔
$CMRO_2$ reduction	↓↓	↓	↓	↓	↓
MAP	↓↓	↓	↓	↓	↓↓

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↑ modest increase, ↑↑ pronounced increase, ↔ no clear effect, ↓ modest decrease, ↓↓ pronounced decrease, +++ very favorable, ++ favorable, + not favorable, *CBF* cerebral blood flow, *$CMRO_2$* cerebral metabolic rate of oxygen consumption, *ICP* intracranial pressure, *MAP* mean arterial pressure

subjects an infusion of propofol at 6 mg/kg/h for 40 min may result in a decrease of $CMRO_2$ up to 34 % [23].

Cerebral metabolism is globally decreased by one-third to one-half of normal in the severely head-injured patient, usually because of the lower metabolic expenditure associated with coma and/or superimposed hypoxia/ischemia, primarily due to secondary insults. Sedation strategies should be designed to depress either the basal or activation components of cerebral metabolism. Common agents used to achieve this goal include central nervous system depressants, such as propofol, benzodiazepines, barbiturates, and similar drugs.

The metabolic suppression of $CMRO_2$ is dose dependent until the electroencephalogram becomes isoelectric. Beyond this level, no further suppression of cerebral oxygen consumption occurs, and the minimal consumption for cellular homeostasis persists.

Effects on Cerebral Blood Flow

When selecting sedative drugs, the maintenance of sufficient cerebral blood flow and at the same time the provision of sedation are paramount and should be considered. For example, cerebral blood flow measured by positron emission tomography is reduced with propofol [24, 25].

Propofol further decreases cerebral blood volume and, in turn, intracranial pressure. This makes propofol most suitable for patients with reduced intracranial compliance [23–25].

The effects of intravenous sedatives on cerebral blood flow (CBF) have primarily been investigated for diazepam, midazolam, and propofol. All of these agents cause a dose-dependent decrease in $CMRO_2$ and CBF. However, the decrease of intracerebral vascular resistance results in a decrease in intracranial pressure (ICP).

Because of its pharmacokinetics, specific effects on cerebral hemodynamic variables, and at the same time preservation of autoregulation and vasoreactivity to carbon dioxide, propofol approximates the ideal sedative more than benzodiazepines. An intravenous bolus produces a dose-dependent, coupled decrease in CBF and $CMRO_2$, similar to that described using barbiturates. The effects on CBF are probably secondary to a reduction in $CMRO_2$. A strong linear correlation between CBF and $CMRO_2$ has been demonstrated [23] using propofol. In experimental studies, escalating propofol doses lead to burst suppression on the electroencephalogram with a decrease of CBF by 38–58 % and $CMRO_2$ by 22 to 43 %. Similar results may be achieved with the use of short-acting semisynthetic narcotics. In humans, EEG burst suppression ratios of 50 and 100 % can be obtained with propofol and remifentanil, respectively, with a proportional reduction of CBF velocity of 22 and 33 % and no changes in arteriovenous oxygen saturation difference, suggesting intact flow–metabolism coupling [23–27].

All sedative agents may cause a decrease in mean arterial blood pressure by inducing both cardiac depression and peripheral vasodilatation. The decrease in blood pressure can cause an increase in intracranial pressure as a result of autoregulatory compensation and, consequently, a reduction in CPP. The hemodynamic effects are usually dose dependent. Therefore, it is important to assess the preload status of the patient to predict the hemodynamic response of the sedative agent, in consideration of cardiac function, and the concurrent use of hyperosmotic agents. When compared with propofol, midazolam is associated with less hypotension but a more variable interval for recovery after the cessation of the infusion [28–34]. Propofol causes more cardiovascular depression when the patient needs to be rapidly induced for general anesthesia; the major cardiovascular effect of propofol is a profound decrease in mean arterial pressure, resulting from a decrease in systemic vascular resistance, cardiac contractility, and preload. A bolus of 2–2.5 mg/kg propofol results in a 25–40 % reduction in systolic blood pressure. This potent effect on mean arterial pressure may affect CPP by one of two mechanisms. If autoregulation is intact, a reduction in mean arterial pressure will produce reflex cerebral vasodilatation and a possible increase in intracranial pressure. Alternatively, if autoregulation is impaired, hypotension may produce a critical decrease in CPP and CBF. The risk of hypotension is greatest in the presence of hypovolemia [35] and should always be considered when this drug is used in bloused in the NICU.

Some additional concerns regarding the use of propofol in the NICU arise from case reports describing cardiac failure in head injury patients receiving long-term propofol infusions and propofol infusion syndrome (PRIS) [35–37]. The combination of anesthetic rather than sedative doses of propofol for controlling intracranial hypertension and the association of vasopressors to maintain CPP are the possible causes of the development of adverse fatal events. Based on these observations, long-term infusion of propofol at dosages higher than 5 mg/kg/h is discouraged in the ICU. Opioids, like benzodiazepines, have little hemodynamic effect on euvolemic patients. When opioids and benzodiazepines are administered concomitantly, they may exhibit a synergistic effect on hemodynamics. The reasons for this synergy are not entirely clear.

The cerebral physiologic effects of opioids are controversial. Morphine-related increases in CBF, described in early reports, were probably secondary to an increase in arterial carbon dioxide tension resulting from respiratory depression. In general, opioids slightly decrease $CMRO_2$, CBF, and intracranial pressure, as long as normocapnia is maintained by mechanical ventilation. Opioids can produce short-lasting, mild decreases in mean arterial pressure, followed by decreases in CPP. In particular, remifentanil may cause decreases in both cerebral metabolic rate and intracranial pressure, with minimal changes in CPP and cerebral blood

flow [38]. Opioids lead to dose-dependent, centrally mediated respiratory depression, which may be profound. The carbon dioxide response curve is shifted to the right, and the ventilatory response to hypoxia is obliterated. For this reason, in intubated spontaneously ventilating NICU patients, if opioids are administered, strict end-tidal carbon dioxide trend monitoring or frequent blood gas analysis must be implemented to identify rapid onset of respiratory depression.

Intracranial Pressure Control

Adequate control of the intracranial pressure (ICP) is one of the main therapeutic goals of managing the critically ill neurologic patient: sedatives may reduce ICP by different mechanisms. In the injured brain, cerebral circulation autoregulation is frequently impaired. Therefore, agitation and associated blood pressure elevations may cause intracranial pressure surges; moreover, the severely agitated patient will have an enhanced cerebral metabolism.

Severe agitation and coughing as in the case of intolerance of the endotracheal tube may increase intrathoracic pressure, reducing jugular venous outflow. In this situation, cerebral metabolism and CBF are increased and venous return is decreased. The additive effect of these phenomena can lead to deleterious increases in intracranial pressure. As cerebral perfusion pressure (CPP) is reduced, additional cerebral vasodilator cascade can reduce it even further. Adequate sedation of an agitated NICU patient with a borderline CPP will block this cascade [7, 10, 11].

As previously described, most of the sedatives used in the NICU decrease the cerebral metabolic rate of oxygen consumption ($CMRO_2$), producing a reduction in CBF, a reduction of cerebral blood volume (CBV), and a decrease in intracranial pressure. The applicability of this concept is not only limited to traumatic brain injury patients but also can be extended to patients with stroke and subarachnoid hemorrhage [17].

Seizures Suppression

Seizures are a frequent event in neuroinjury patients [39–41]. Convulsive and nonconvulsive seizures occurred in 22 % of the traumatic brain injury cohort and in 15 % of patients with intracerebral hemorrhage or subarachnoid hemorrhage [17]. Seizures produce a massive increase in cerebral metabolism and possibly a mismatch between oxygen delivery and metabolism in the brain area affected. Together with antiepileptic drugs, sedation appears to be an attractive option in reducing seizures in the NICU.

Benzodiazepines increase the seizure threshold and are useful anticonvulsants [42, 43]. In fact, in all settings benzodiazepines are a first-line treatment of a new onset of seizures.

The ability of propofol to protect against seizures has provided conflicting data [29, 43]. More recent studies showed that standard or high-dose propofol infusion (2 mg/kg induction bolus followed by 150–200 μg/kg/min infusion) can be reliably used as an anticonvulsant, even for the control of status epilepticus [31–34]. Experimental data have shown propofol to have strong anticonvulsant properties, which have proved to be very effective in controlling refractory status epilepticus. A recent statement by the European Federation of Neurological Societies included the use of propofol as an antiepileptic for convulsive epileptic status in the ICU setting [33].

Current Use of Sedative and Analgesic Agents

Propofol

Propofol (2, 6-diisopropylphenol) is a potent intravenous hypnotic agent which is widely used for the induction and maintenance of anesthesia and for sedation in the ICU. At room temperature, propofol is an oil and insoluble in aqueous solution. Present formulations consist of 1 or 2 % propofol, 10 % soybean oil, 2.25 % glycerol, and 1.2 % egg phosphatide. Edetate disodium (EDTA) or metabisulfite is added to retard bacterial and fungal growth.

Propofol is a global central nervous system depressant. It directly activates GABA receptors. In addition, propofol inhibits the NMDA receptor and modulates calcium influx through slow calcium ion channels. Propofol has a rapid onset of action with a dose-related hypnotic effect.

Propofol is highly lipophilic with a large volume of distribution. This property results in rapid uptake and elimination from the CNS, resulting in rapid onset of action and rapid recovery when discontinued.

In a recent investigation, patients with a higher sequential organ failure assessment (SOFA) were more likely to show a deeper level of sedation when on propofol [38]. In another study, it was demonstrated that the offset of propofol activity can vary considerably and is related to the depth of sedation, the duration of the infusion, and patient size. In non-neuroinjured patients, the predicted emergence time (full awakening and normal orientation) from a deep sedation (Ramsay 4) averaged 25 h for a 24-h infusion but increased to nearly 3 days for propofol infusions lasting 7–14 days [44].

A recent prospective study showed that, in medical patients requiring >48 h of mechanical ventilation, sedation with propofol results in significantly fewer ventilator days compared with intermittent lorazepam when sedatives are interrupted daily [45], one possible explanation being the shorter half-life of propofol, relative to lorazepam.

Propofol, a pure sedative–hypnotic alkyl phenol, exhibits rapid onset and short duration of action once discontinued after lighter sedation. These characteristics make this agent particularly advantageous in the NICU because it is possible to reduce sedation rapidly to conduct a thorough neurologic examination of the patient. Because of rapid central nervous system penetration and subsequent redistribution after a single dose, the onset of action of propofol is rapid (1–2 min), and its effect is brief (10–15 min). For this reason, propofol must only be administered by continuous infusion when used for sedation. Propofol is very lipid soluble, has a large volume of distribution, and can be given for prolonged periods of time without significant changes in its pharmacokinetic profile. Because propofol has no active metabolites, the termination of its clinical effect is dependent solely on redistribution to peripheral fat tissue stores. When the infusion is discontinued, the fat tissue stores redistribute the drug back into the plasma but usually not reaching clinically significant levels. Emergence from light level of sedation with propofol in ICU patients varies with the duration of sedation, with a slightly longer recovery reported after more than 12 h of infusion; however, it is rare for the effect to last longer than 60 min after the infusion is stopped.

Opioids

Analgesia is required in almost all NICU patients, and morphine derivatives appear to be an appropriate choice. Morphine, fentanyl, and remifentanil are the opioids that are most frequently used in the ICU [46]. Opioids stimulate the μ-, κ-, and δ-opioid receptors, which are distributed within the central nervous system. The μ-receptor is the primary site of opioid activity and is subdivided into the μ1- and μ2-subreceptors. Stimulation of the μ1-subreceptor leads to inhibition of neuronal pain [25]. Morphine, with its prolonged duration of action, and meperidine and its metabolite, normeperidine, which can precipitate seizures, are not ideal analgesics in the NICU setting. Normeperidine use is also associated with neuroexcitatory effects including tremor, delirium, and seizures [26].

The intravenous route of administration is preferred because it allows a faster onset and better titrability [27]. Fentanyl, with high lipid solubility, has a very rapid onset and a short duration of action after a single dose because of redistribution into peripheral tissues. Caution must be exercised, however, as the pharmacokinetics are altered with prolonged administration. Moreover, fentanyl is a substrate CYP3A4 and is affected by CYP3A4 inducers, such as phenytoin, which is frequently used in the NICU [25]. Genetic factors have been shown to regulate both opioid pharmacokinetics and pharmacodynamics and could be the reason for the variability in response to opioids that is observed in clinical practice [47].

Remifentanil has unique pharmacokinetic properties that make it attractive for use in neurocritical care. It has an ester structure that makes it susceptible to very rapid hydrolysis by nonspecific esterases in blood and tissue, with lack of drug accumulation following repeated boluses or continuous infusion. Remifentanil has a rapid blood–brain equilibration time (1.0 and 1.5 min), and its context-sensitive half-time is also short, i.e., 3–5 min. This time is unaffected by the duration of the infusion. Remifentanil has potential for use as an analgesic agent and, because of its ultrashort duration of action, requires the use of a continuous infusion [35–37, 48, 49].

Remifentanil is metabolized directly in the plasma by nonspecific esterases. The primary metabolite is remifentanil acid, a compound with little pharmacologic activity. Remifentanil acid is eliminated by the kidneys, and the action of remifentanil is not prolonged by renal injury. In addition, dose adjustments are not required in patients with hepatic dysfunction. Because of its short half-life, remifentanil has unique pharmacokinetic properties that make it attractive for use in neurocritical care. It may facilitate frequent awakening to evaluate neurologic and respiratory parameters [50]. In a study of patients with traumatic brain injury who were mechanically ventilated, remifentanil was used for on-top analgesia in head trauma patients without adverse effects on cerebrovascular hemodynamics, cerebral perfusion pressure, or intracranial pressure [51].

Benzodiazepines

Benzodiazepines such as midazolam, lorazepam, and diazepam are sedatives widely used in the ICU. They have anxiolytic, sedative, and hypnotic properties. Benzodiazepines experimentally increase the frequency of opening of the $GABA_a$ chloride channel in response to binding of GABA [52]. These pharmacologic effects depend on the degree of the binding of benzodiazepines to the GABA receptor; effects include anxiolysis, sedation, muscle relaxation, anterograde amnesia, respiratory depression, and anticonvulsant activity.

Midazolam, with its high clearance and short half-life, is a useful alternative to propofol [29–31, 42, 53–55]. However, a continuous infusion of midazolam for more than 24 h will cause the loss of rapid recovery properties; the known explanation for this phenomenon is the accumulation of active metabolites. Therefore, midazolam, administered via titrated continuous infusions, is recommended only for short-term use, as it produces unpredictable awakening when infusions continue for longer than 48–72 h. Moreover, the pharmacokinetics of midazolam change considerably when it is administered via continuous infusion to critically ill patients for extended periods of time (>24 h). This lipid-soluble drug undergoes oxidation in the liver via the CYP450 enzyme system

to form water-soluble hydroxylated metabolites, which are excreted in the urine. The primary metabolite of midazolam, 1-hydroxymidazolam glucuronide, has central nervous system (CNS) depressant effects and may accumulate in the patient who is critically ill, especially if kidney failure is present. Also, the drug accumulates in peripheral tissues, particularly in obese subjects, as well as in the bloodstream and is not metabolized. When the drug is stopped, peripheral tissue stores release midazolam back into the plasma, and the duration of clinical effect can be prolonged.

In one study in patients on prolonged sedation, elevated levels of 1-hydroxymidazolam glucuronide were detected an average of 67 h after the midazolam infusion was discontinued [56].

These properties are reflected in the 2002 recommendation of Society of Critical Care Medicine (SCCM) consensus guidelines, where it was stated that midazolam be used only for short-term (<48 h) therapy and that lorazepam should be used for patients in the ICU requiring long-term sedation [57]. A randomized controlled trial compared lorazepam with midazolam for long-term sedation and found no difference in the time to awakening between the groups [58].

Numerous factors affect the response to benzodiazepine and include age, concurrent pathology, prior alcohol use, and therapy with other sedative drugs. Also, recent studies suggested that there is a genetic variability in the response of patients to benzodiazepines [59].

Recent reports have alerted clinicians to the risks for toxicity related to propylene glycol (a diluent used to facilitate drug solubility) accumulation in patients receiving intravenous lorazepam [60]. Toxicity of propylene glycol may cause hyperosmolar states, cellular toxicity, metabolic acidosis, and acute tubular necrosis. It has been proposed to use the osmolar gap as a surrogate marker for serum propylene glycol concentration. In critically ill patients receiving lorazepam for sedation, an osmolar gap above 10 was associated with concentrations previously reported to cause toxicity [61].

Ketamine

Ketamine is nonbarbiturate phencyclidine that provides analgesia and anesthesia with relative hemodynamic stability and is frequently used during hemorrhagic shock [62]. However, due to the known effects on CBF and ICP, this drug has found very little application in the neurosurgical ICU setting [63, 64]. Potential side effects of ketamine are increase of $CMRO_2$, CBF, and ICP.

In other reports, ketamine was shown to decrease CBF and ICP in head trauma patients sedated using both ketamine and propofol or with a $PaCO_2$ maintained constant [65], and in an experimental setting ketamine even had neuroprotective properties [66]. The potential advantages of using ketamine in traumatic brain injury patients are maintenance of hemodynamic status as well as CPP, with absence of withdrawal symptoms. One study investigated the cerebral hemodynamics of ketamine used for sedation of severe head injury patients. Ketamine was compared with sufentanil as an analgesic, either in combination with midazolam and showed comparable effects in maintaining intracranial pressure and cerebral perfusion pressure of severe head injury patients under controlled mechanical ventilation [67]. Larger clinical trials are needed to test the potential side effects of ketamine in the brain-injured patient before recommending the use in routine clinical practice.

Dexmedetomidine

Dexmedetomidine (DEX) is a new drug that has been recently introduced into clinical practice [68–71]. It is a selective α-2 agonist that provides anxiolysis and sedation without causing respiratory depression. Dexmedetomidine has analgesic, hypnotic, and anxiolytic effects.

Dexmedetomidine is the dextro enantiomer of medetomidine, with a specificity for the α-2 receptor, which is seven times that of clonidine, the agonist for the α-2 receptor subtypes that mediates the effects of dexmedetomidine.

Dexmedetomidine has an onset of action approximately 15 min after intravenous injection and reaches peak concentrations in 1 h after continuous IV infusion.

The pharmacokinetics of DEX is largely influenced by liver rather than renal function. DEX is metabolized in the liver through glucuronide conjugation in the cytochrome P450 enzyme system. There are no known active or toxic metabolites; hepatic clearance may be decreased in patients with severe liver disease, although it is less affected by renal disease [72].

Other studies investigated the immune, cardiovascular, and respiratory response of varying doses of dexmedetomidine in healthy, young human volunteers. Dexmedetomidine-induced dose-dependent decreases in systolic and diastolic blood pressure and in heart rate and plasma norepinephrine levels [73–77]. Some studies reported a transient hypertensive response after IV high-dosage boluses, because of activation of peripheral vascular alpha-2 receptors before the central sympatholytic effect. Only minimal effects of dexmedetomidine on the respiratory system were observed throughout a broad range of plasma concentrations [78].

At present time, the FDA-approved duration of infusion of dexmedetomidine remains 24 h.

In October 2008, dexmedetomidine was FDA-approved for procedural sedation in nonintubated patients.

The peculiarity of sedation with DEX in comparison to propofol and midazolam is the easy arousability of patients under sedation: it is possible to reach a "cooperative sedation" during which patients may still be arousable during procedures or respond to neurologic testing during craniotomies [79].

DEX has some concerning effects on cerebral circulation. DEX sedation in volunteers seems to cause a decrease in regional and global cerebral blood flow [80], but the ratio with CMRO2 and flow metabolism coupling is maintained [81]; MRI studies showed that the cerebral blood flow pattern is similar to what is observed in natural sleep [82]. Low-dose dexmedetomidine showed an additive effect with meperidine on lowering the shivering threshold [83]. The neuroprotective properties of DEX have been investigated, and animal studies showed a preconditioning effect and attenuation of ischemia–reperfusion injury [84].

Similarly to clonidine, DEX has been used in the treatment of withdrawal from drugs (cocaine, alcohol, opioids); the mechanism could be the counterbalance of the central hyperadrenergic states induced by the withdrawal; in one study DEX was used successfully to control withdrawal in patients with history of cocaine and opioid abuse undergoing cerebral angioplasty for cerebral vasospasm [85, 86].

Barbiturates

Currently, barbiturates are used in the NICU only in specific conditions.

Barbiturates are associated with high incidence of systemic complications (i.e., hemodynamic instability, immunosuppression, hyper-/hypokalemia, atelectasis) and an unfavorable pharmacodynamic profile given that they accumulate in peripheral tissues after long-term infusions, leading to prolonged recovery from sedation. Thus, they are recommended only as second-tier therapy for refractory intracranial hypertension [87]. The other indication for barbiturates is the treatment of refractory status epilepticus as described in the most recent guidelines issued by the European Federation of Neurological Societies (EFNS) [88].

Side Effects of Sedative Agents

Propofol

While propofol lacks analgesic properties, it holds many of the characteristics of an "ideal" sedative. For this reason it should not be used alone during sedation for painful procedures. Concerning its hemodynamic effect, propofol induces both vasodilatation and a negative inotropic effect and by these mechanisms may cause hypotension of various grades of severity. The hypotensive effect of propofol may be pronounced in hypovolemic patients or in patients with a reduced cardiac output (such as those on other cardiodepressant medications) and in the elderly. Thus, when used to sedate patients affected by acute neurological injuries, propofol may decrease cerebral perfusion pressure even if it induces a decrease in ICP [89]. Moreover, propofol may potentiate the cardiodepressant effects of alcohol, opioids, benzodiazepines, barbiturates, antihypertensives, and antiarrhythmics. When used in the NICU at high doses (i.e., as a first-line therapy for intracranial hypertension or for EEG burst suppression), invasive blood pressure and even cardiac output monitoring may be necessary to monitor the hemodynamic adverse effects.

Propofol causes a dose-dependent respiratory depression: during bolus or continuous infusions, continuous monitoring of pulse oximetry, respiratory rate and depth of respiration, and blood pressure are recommended. Propofol is insoluble in water and is suspended in an emulsion of soy, glycerol, and egg phospholipids; these components are susceptible to bacterial contamination, regardless of the presence of disodium edentate or EDTA as bacteriostatic agents. The carrier solution frequently causes pain at the injection site. This effect can be lessened by administration through a central or larger vein or by premedication with IV lidocaine in the same vein.

The emulsion carrier contains egg and soy proteins and can be responsible for rare immunologic reactions in patients with severe allergic reactions to these food substances.

One common side effect, particularly after prolonged high-rate infusions in the ICU, is hypertriglyceridemia, which is caused by the lipid vehicle. Moreover, the lipid vehicle contains 1.1 kcal/mL, which should be taken in consideration when computing the nutritional metabolic requirement.

Recently, propofol-related infusion syndrome' (PRIS) has been described in pediatric and adult patients receiving doses greater than 80 mcg/kg/min for prolonged periods of time. The exact mechanism of PRIS is still unclear, but the clinical signs include metabolic acidosis, hyperkalemia, rhabdomyolysis, hypoxia, and progressive myocardial failure [90–92]. Monitoring for electrolytes and increases in lactic acid, creatinine kinase, and triglycerides is recommended in patients receiving high doses >50 mcg/kg/min for longer than 48 h. All these laboratory parameters should be checked at least once daily for patients at risk. A hospital policy limiting the use of propofol to a safe limit is recommended.

Benzodiazepines

Their anticonvulsant properties make benzodiazepines a first-line treatment option for acute management of seizures and status epilepticus. However, tolerance can occur rapidly leading to the need for increasing the dose to maintain efficacy. Benzodiazepines are pure sedative agents, with no analgesic properties; thus, analgesia should be added when pain is a concern. IV benzodiazepine may cause hypotension and increased heart rate at higher dose and, in susceptible patients, hypovolemia, low cardiac output state, or severe vasodilation. High doses of benzodiazepines may cause

respiratory depression and apnea, leading to an elevation in ICP caused by hypercarbia.

Benzodiazepine sedation overdose is not uncommon in neuroinjury patients. Risk vs. benefit of benzodiazepine use in the neuroICU should be carefully evaluated after prolonged infusions (48–72 h) or in patients with altered renal function. Flumazenil can reverse the effects of benzodiazepines, but it should be used carefully because of the risk of lowering seizure threshold and an increase in ICP.

Another major side effect of benzodiazepines, delirium, is discussed later in this chapter.

Opioids

Opioids do not have a direct effect on ICP or cerebral blood flow. However, when they act as respiratory depressants may cause hypercarbia with consequent increase in ICP. For this reason, all patients receiving narcotics in the NICU should receive continuous monitoring of respiratory rate and pulse oximetry with lowest possible FiO_2 to avoid late unmasking of hypercarbia.

Other common adverse reactions to narcotics include histamine release causing urticaria and flushing, somnolence, respiratory depression, chest wall and other muscle rigidity (primarily with fentanyl and remifentanil), dysphoria or hallucinations (primarily with morphine), nausea and vomiting, GI dysmotility, and vasodilatation with hypotension. Full anaphylactic shock is extremely rare. Opioids can be reversed by their antagonist, naloxone, which should be titrated slowly and in low doses first to avoid an "overshoot" phenomenon that can result in a catecholamine peak leading to hypertension, tachycardia, and emergence agitation. This reaction can exacerbate intracranial hypertension.

Dexmedetomidine

The most common adverse effects of dexmedetomidine include dry mouth, bradycardia, hypotension, lightheadedness, and anxiety. Bradycardia and hypotension are frequently observed during the initial loading dose; thus, arterial pressure and cerebral perfusion pressure should be continuously monitored. DEX does not have a significant effect on ICP. Hypotension and bradycardia can be exacerbated by concomitant administration of antihypertensive and antidysrhythmic medications.

Monitoring Sedation in the NICU

Monitoring the level sedation in the NICU is crucial. The improper use of sedatives in dosages either too high or too low may affect the neurological examination and may lead to the wrong neurological diagnosis. Oversedation increases the risk of infections by delaying weaning from mechanical ventilation, and the increased length of stay is associated with increased costs. By contrast, an undersedated patient may be agitated, anxious, and at risk for self-extubation, recalling unpleasant events or simply desynchronizing with mechanical ventilation.

Sedation scales are used to evaluate arousal, depth of sedation, and response to stimuli [93]. The Ramsay Scale evaluates consciousness, while the Richmond Agitation–Sedation Scale (RASS) examines cognition; Sedation Agitation Scale (SAS) and the Motor Activity Assessment scale (MAAS) monitor sedation and arousal. The use of sedation scales can reduce the amount of sedatives given to achieve a specific sedation target, decreasing the number of days on mechanical ventilation and cost of hospital stay [94], but no validation is available in the neuroICU environment.

Recently, processed electroencephalogram (EEG) algorithms have been introduced into clinical practice as a method to monitor objectively and quantitatively the level of consciousness in ICU patients. One example is the determination of bispectral index (BIS) [95], which has been associated with a decrease in sedative use in intraoperative care [96], but never validated in neurocritically ill patients.

Delirium in the NICU

Delirium is an acute brain dysfunction, defined as an acute disturbance of consciousness accompanied by inattention, disorganized thinking, and perceptual disturbances that fluctuate over a short period of time [97]. Numerous risk factors have been described [98–101]:

- Host factors age, baseline comorbidities, baseline cognitive impairment, and genetic predisposition
- Factors related to the acute illness: sepsis, hypoxemia and metabolic disturbances, primary central nervous system disease, shock, liver disease, acute respiratory distress syndrome, postoperative status, kidney disease, heart failure, and anemia
- Iatrogenic and environmental factors, metabolic disturbances, anticholinergic medications, sedatives and analgesic medications, and sleep disturbances

The American Psychiatric Society has published its guidelines on delirium, which included a list of substances that can cause delirium through intoxication or withdrawal, including sedative agents and analgesics [102].

In trauma ICU, sedatives and analgesics were found to be risk factors for development of delirium [103, 104]. Midazolam was an independent risk factor for the development of delirium in both surgical and trauma patients; the association between opioids and delirium was inconsistent, with the use of fentanyl but not morphine as a risk factor for

delirium in surgical ICU patients but not in trauma patients [105, 106]. Similar results were seen in a study performed in burn trauma patients [107]. Again, benzodiazepines were found to be an independent risk factor for the development of delirium.

A recently introduced evidence-based clinical bundle has been suggested as a way to improve patient outcome and recovery [108]. ABCDE stands for awakening and breathing trials, choice of appropriate sedation, delirium monitoring, and early mobility exercise.

Benzodiazepines are known to increase the risk of delirium in a dose-dependent manner. Multiple studies have shown that protocolized target-based sedation and daily spontaneous awakening trials reduce the number of days on mechanical ventilation. This strategy also exposes the patient to smaller cumulative doses of sedatives.

In the critically ill NICU patient, the interruption of sedation may have negative effects because it could also induce a stress response. ICP and the CPP levels can increase during interruption of sedation, when compared to baseline levels recorded during continuous sedation. In the majority of patients, these changes are transient and tolerable. However, in a subset of patients with very low cerebral compliance, the interruption of continuous sedation can induce marked ICP and CPP changes that can produce secondary injuries [109]. Those patients should be excluded from repeated evaluations, and information should instead be gathered from other multimodality monitoring methods in combination with neuroimaging [110].

NICU Sedation and Analgesia: A Suggested Approach

Because no single drug can achieve all of the requirements for sedation and analgesia in the ICU, the use of a combination of drugs, each titrated to specific end points, is usually a more effective approach. This strategy allows lower doses of individual drugs and reduces the problems of drug accumulation. At our institution, we implemented a simplified sedation protocol based on time of presentation of the neuroinjury or ICP:

- In the acute phase (i.e., first 48–72 h or until intracranial hypertension is controlled), a continuous infusion of a combination of propofol (1.5–6 mg/kg/h) and fentanyl (0.5–1.5 μg/kg/h) is used.
- In the subacute phase (i.e., after 72 h or when intracranial pressure is normalized), intermittent boluses of benzodiazepines (in our case, lorazepam 0.05 mg/kg every 2–6 h) follows.

We continue to sedate patients until no ventilatory support is required, and then we taper sedation slowly to prevent withdrawal symptoms in 24–48 h.

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