Chapter 9
Propofol for Sedation of the Critically Ill Child

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Introduction

Propofol is an intravenous (IV) anesthetic medication that modulates gamma-aminobutyric acid-A ($GABA_A$) receptors and inhibits N-methyl-D-aspartate (NMDA) receptors, inhibiting postsynaptic neuronal depolarization with resulting hypnotic, sedative, and amnestic effects [1, 2] as well as dose-dependent side effects, including respiratory depression and hypotension. It is highly lipophilic, readily crossing the blood-brain barrier and diffusing into fatty tissues [2]. Its short half-life makes it a popular option for titratable sedation with over 80% of mechanically ventilated adults receiving continuous IV sedation via propofol only a decade ago [3]. Due to its rapid onset, titratable depth of anesthesia/sedation, rapid offset, and low incidence of adverse events when used by appropriately trained, experienced providers, propofol has become a very popular choice for procedural sedation and anesthesia in pediatrics, including frequent use outside the operating room by non-anesthesia providers. In a review of over 90,000 procedural sedations provided by pediatric critical care medicine physicians using propofol, serious adverse events were reported in 2.2% of encounters, while <1% required airway intervention, and no deaths occurred [4].

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Despite this adult intensive care unit (ICU) and pediatric procedural experience, propofol is less commonly used for continuous sedation in the pediatric intensive care unit (PICU) setting for several reasons. The US Food and Drug Administration issued a label change in 2001 recommending against off-label use of propofol for continuous sedation in the PICU, possibly related to an unpublished industry study that observed increased mortality for children in the ICU receiving propofol vs. standard sedation [5, 6]. Despite the label recommendations, PICU patients are frequently exposed to propofol; 39% in one study received propofol during the ICU stay [7], and exposure increased from 2001 to 2007 [8]. Data on efficacy and clinical outcomes for pediatric patients receiving propofol versus other continuous sedatives in the ICU setting are lacking, and serious safety concerns persist, chiefly related to propofol-related infusion syndrome (PRIS). Acknowledging these concerns, propofol remains an important sedative option for the pediatric intensivist, as its pharmacokinetic and pharmacodynamic properties are ideally suited to certain specific sedation goals.

Pharmacology

Mechanism of Action

Propofol (2,6-diisopropylphenol) is a $GABA_A$-receptor agonist; binding to the receptor increases cellular chloride influx, resulting in hyperpolarization and inhibition of synaptic conduction in the central nervous system (CNS). It also acts on presynaptic GABA receptors, inhibiting GABA reuptake and augmenting its release in animal models. Tonic GABAergic signaling inhibits acetylcholine (ACh) release in multiple brain areas; propofol augments ACh inhibition in the frontal cortex and the hippocampus, resulting in decreased arousal and ultimately loss of consciousness. Other areas of the brain, including the substantia nigra, are also affected [9].

Pharmacokinetics

Pharmacokinetics differ for propofol infusions compared to bolus dosing. In bolus dosing, propofol has a rapid onset of action (10–50 seconds). Offset is related to rapid drug distribution into tissues (9 min) rather than metabolism, which is primarily hepatic [1, 10]. A typical anesthetic induction dose is 1.5–3 mg/kg, divided into two to three doses to allow titration to effect while minimizing dose-related hemodynamic and respiratory side effects. Maintenance of anesthesia is achieved by repeat bolus doses of 0.5–1 mg/kg, an infusion, dosed from 50 to 250 mcg/kg/min [1, 11–15], or both. Higher doses may be needed if propofol is used alone [16, 17]. Younger children may also require higher doses, due to differences in volume of distribution and clearance [1, 11].

Infusion pharmacokinetics (PK) fit a three-compartment PK model, with clearance approximated by hepatic blood flow [18]. With infusions used for maintenance of anesthesia, children require higher doses and have longer context-sensitive half-life for propofol than adults. The half-life doubles from hour 1 of propofol infusion to hour 4 and continues to increase over time due to tissue redistribution [19]. These observations likely also apply to lower-dose infusions employed for continuous sedation. One short-term PICU-based PK study observed pharmacokinetics among 28 patients receiving propofol infusions for up to 13 hours. In this study, the initial propofol bolus dose diffused rapidly into a second and third compartment, both with extremely large volume of distribution, suggesting that a prolonged infusion could result in a very long terminal half-life of the drug. At this duration, average offset time was 15 min, although there was substantial variability among patients [10]. PK modeling data suggest that the offset following prolonged infusion varies by depth of sedation and duration of infusion and could take over 3 days for infusions lasting 7–14 days [20]. Longer recovery has been observed with long-term infusions of propofol in adult patients, with offset times of up to 24 h [21].

Besides targeted depth of sedation and infusion duration, additional clinical factors may impact the clearance and offset following prolonged infusion. Critically ill adults have decreased clearance, attributed to lower hepatic blood flow from shock [22, 23]. Patients treated with therapeutic hypothermia (33–34 degrees) also have decreased propofol clearance [24]. Unlike other options for continuous pharmacologic sedation, renal dysfunction, obesity, and liver dysfunction are not associated with delayed awakening after receiving propofol [23].

Pharmacodynamics

Commonly recognized systemic effects of propofol are dose-dependent and include CNS depression, ranging from anxiolysis to anesthesia; respiratory depression, ranging from hypoventilation to apnea [25]; upper airway obstruction [1]; and hemodynamic effects including vasodilation, decreased cardiac index, and hypotension [26, 27]. Other properties include antiemetic [28, 29] and anticonvulsant effects [30, 31], which can be additionally beneficial in certain patient populations. The hemodynamic effects of propofol result in decreased cerebral blood flow (CBF); this, combined with a decrease in cerebral metabolic demand, results in decreased intracranial pressure (ICP) [32, 33]. Despite the decrease in CBF, cerebral tissue oxygenation is preserved, due to an accompanying decrease in cerebral metabolic demand [26]. Up to 60% of patients experience pain at the injection site. Propofol does not provide any analgesic effect, so it is often paired with opioids or ketamine for painful procedures, which can alter systemic side effects and decrease the dose of propofol needed to achieve adequate sedation [1, 34]. This is also true when used for continuous sedation in the ICU; using propofol alone is associated with increased agitation in ventilated adult trauma patients [35] compared to its use in combination with other agents.

Nutritionally, propofol can contribute a significant amount of calories from fat when used for continuous sedation in adult ICU patients. In one study, propofol provided an average of 46 +/− 117 kcal/d in ICU patients receiving this drug. Fat from propofol constituted an average of 17% of total energy intake, and provided up to 100% for some patients during the first ICU days, which may be disadvantageous; among survivors, proportion of calories due to fat intake was associated with prolonged ventilation time [36]. Hypertriglyceridemia occurs in 18% of adults receiving propofol for over 24 h; in one study, 10% developed pancreatitis [37]. For pediatric calculations, an infusion of 50 mcg/kg/min (3 mg/kg/hr) provides 7.9 kcal/kg/day.

With prolonged (>24 h) exposure, evidence suggests an increased risk of ICU-acquired weakness in adult patients with sepsis and respiratory failure receiving propofol compared to other sedatives (OR = 3.4) [38]. This may be a consequence of impaired mitochondrial activity, also shown to be the mechanism behind PRIS [39]. In vitro, propofol profoundly impairs fatty acid oxidation in skeletal muscle cells, even at low doses [40]. Animal model studies demonstrate impaired neutrophil chemotaxis, phagocytosis, and bacterial clearance with propofol exposure [23]. It is also associated with impaired neutrophil oxidative response in vitro, although studies have not identified this effect in vivo after short exposures [41].

Finally, prolonged infusions raise concerns regarding the potential toxicity of diluents and preservatives in the propofol formulation, which differ by manufacturer. Egg phosphatide, soybean oil, and sulfites may be present and precipitate allergy or anaphylaxis, although this is uncommon in newer formulations. Disodium EDTA can cause hypocalcemia, and the lipid emulsion can cause hypertriglyceridemia, pancreatitis, phlebitis, fat emboli (particularly in sulfite-containing formulations), and solubility and compatibility issues; it may also be associated with the development of PRIS [23]. It is unknown how frequently these complications occur in patients on prolonged propofol infusions, but they are likely dose- and duration-dependent.

Clinical Considerations for Use

Indications for Short-Term, Deep Sedation

Continuous sedation in critically ill patients should follow adequate treatment of pain, should be targeted to a prescribed goal, and should be minimized when possible. Targeting a light, rather than deep, level of sedation is associated with improved outcome in adult ICU patients, including shorter time to extubation, less frequent tracheostomy, and reduced length of stay [42]. Targeting a light level of sedation can be safe and feasible in the pediatric population [43, 44].

The pharmacologic properties of propofol are well-suited to certain specific sedation goals. For short-term use compared to dexmedetomidine, propofol achieves a greater depth of sedation with a faster offset [45]. Similarly, ventilated adult ICU

patients receiving propofol for continuous sedation were more frequently able to achieve deep sedation or coma (RASS ≤-4) as a targeted depth of sedation, compared to patients receiving dexmedetomidine [46]. Therefore, propofol can be ideal for patients who require deep sedation for short periods of time (e.g., young patients who require several hours of immobility after arterial access for interventional procedures). Deep sedation or coma may benefit some patients with increased ICP. Propofol reduces cerebral metabolic demand and reduces ICP, although if hypotension occurs, this may reduce cerebral perfusion pressure, which would limit the acceptable propofol dose for that patient [26, 32, 33].

Due to its fast offset with bolus and short-term anesthetic dosing, propofol is an attractive option for patients who require sedation but who also require intermittent interruption of sedation for neurologic examination, or as a short-term bridge to allow other sedatives to be weaned for extubation. However, propofol is only a good option for these indications for a short time frame. Patients with neurologic injury have increased risk of PRIS (described in detail below,) and due to the pharmacokinetics of propofol infusion, the offset time is expected to increase with longer infusion times [20].

Propofol "Drug Washout"

Pediatric ICU patients who require prolonged analgosedation with opioids and benzodiazepines are at high risk of developing tolerance and opioid-induced hyperalgesia, resulting in ineffective symptom control despite escalating doses [47, 48]. By employing a different class of medication, an intermittent transition to propofol could theoretically allow periodic interruption of opioids and benzodiazepines to reduce tolerance and improve efficacy. It is unknown how much reduction of tolerance would be achieved within the time and dose range generally considered safe for continuous propofol infusion. To date, no clinical evidence supports the use of propofol in this role.

The Impact of Propofol on Sleep and Delirium in ICU Patients

While propofol readily achieves deep sedation, it has negative impacts on physiologic sleep. The proportion of patients achieving rapid eye movement (REM) sleep, and the amount of time spent in REM sleep, is decreased when patients are receiving propofol compared to other sedatives [49]. Patients receiving continuous propofol infusion lose normal circadian cycling [50]. Altogether, sleep in patients sedated with propofol has been evaluated in only a handful of small studies, and a recent Cochrane review [51] concluded that evidence suggests no beneficial effect. Early adult studies suggested that, compared to benzodiazepine-based sedation, propofol was associated with less delirium in ICU patients [52, 53]. However, subsequent

research has found that, compared to propofol and benzodiazepines, dexmedetomidine is associated with even less delirium and coma [54–56]. The depth of sedation achieved may be partly responsible; propofol exposure, as well as hours under deep sedation, is independently associated with delirium in adults [57].

Palliative Sedation

Providing relief of pain, dyspnea, anxiety, and other symptoms at the end of life is a crucial component of critical care. Palliative sedation refers to "the use of sedative medications to relieve intolerable and refractory distress by the reduction in patient consciousness" [58]. While maintaining consciousness and the ability to interact with loved ones is often a goal at the end of life, if standard medications fail to alleviate symptoms, prioritizing the relief from suffering may outweigh the preservation of consciousness. In this setting, palliative sedation may be consistent with a patient and family's goals. Propofol has been successfully used, in addition to benzodiazepines and opiates, for palliative sedation in both children and adults. Propofol offers a rapid onset, the opportunity to titrate to a deep level of sedation if required, and some beneficial side effects including antiemetic properties. Unfortunately, its narrow therapeutic index typically requires a critical care setting for administration. In published pediatric case series, propofol for palliative sedation has been used for up to 30 days, with infusion doses ranging from 12 to 200 mcg/kg/hr, with reports of good symptom control and both family and provider satisfaction [59, 60]. For a more in-depth discussion of palliative analgesia and sedation, the reader is referred to that specific chapter (Chapter 22).

Propofol-Related Infusion Syndrome (PRIS)

In 1992, a case series was published describing a clinical syndrome of metabolic acidosis, bradyarrhythmia, progressive myocardial failure, and death among five children receiving propofol infusion (>83 mcg/kg/min for >48 h) [61]. This syndrome, PRIS, is estimated to occur in about 1% of patients receiving propofol infusion, but it can be irreversible once identified, with 18–30% mortality among those affected [62]. Other symptoms include rhabdomyolysis [63, 64], elevated cardiac enzymes, inverted T wave [65], hyperkalemia [66], elevated serum acylcarnitines [67], and Brugada-like electrocardiographic pattern (ST segment elevation in the precordial leads) [68]. Risk factors include pediatric age; concurrent vasopressor therapy; higher Acute Physiology, Age, Chronic Health Evaluation (APACHE) score (in adults); and neurologic injury including seizure and traumatic brain injury [63, 69]. The risk is primarily dose- and duration-dependent [70], but cases have

been reported in patients receiving <4 mg/kg/hr (=67 mcg/kg/min). Diagnosis can be difficult and the presenting symptoms may be sudden arrhythmia development or cardiac arrest [69]. Unfortunately, biochemical monitoring does not prevent all cases; one case report describes fatality despite negative screening creatinine kinase and lactate [71]. The largest case series, examining over 1000 patients with suspected PRIS, described 10% mortality among patients deemed to be low risk; mortality for the highest-risk patients approached 90% [63].

Pathophysiology

Propofol interferes with free fatty acid metabolism and mitochondrial respiratory pathways. In multiple human cell types in vitro, propofol interferes with mitochondrial complexes I–III, resulting in a metabolic switch from oxidative phosphorylation to glycolysis, increasing the generation of reactive oxygen species, and causing apoptosis [72]. Propofol also inhibits the enzyme carnitine palmitoyltransferase I (CPT1), preventing mitochondrial metabolization of free fatty acids, resulting in structural changes and deposition of free fatty acids in cardiac and hepatic tissues [67]. Even at low-dose exposures, skeletal muscle cells demonstrate impaired fatty acid oxidation and mitochondria have reduced spare electron transfer chain capacity [40]. Decreased utilization of free fatty acids as an energy source results in myocardial fat deposition, which has been observed at autopsy in affected patients [73].

Prevention and Treatment

Consensus in the literature and across international institutional practice is that propofol infusions are generally considered safe when limited to doses <4 mg/kg/hr (= 67 mcg/kg/min) and duration <24–48 hours [74, 75]. In one study of 210 pediatric patients after introduction of an institutional policy with good adherence to these limits (98% of infusions were used for <24 h, and 87% were dosed at <4 mg/kg/hr (= 67 mcg/kg/min)), no full cases of PRIS occurred, although 8% still developed at least one symptom consistent with PRIS [76]. Additional recommendations for prevention include using dextrose infusion to suppress fat metabolism and avoiding propofol in high-risk patients, including those with neurologic injury, vasopressor requirements, or shock [23]. Screening patients for rhabdomyolysis and limiting use to those with low CK may also help [77]. In obese patients, doses should be based on predicted/ideal body weight to avoid inadvertent dose-related toxicity [78].

The cornerstone of treatment is discontinuing propofol as soon as toxicity is recognized. Case reports describe successful treatment with invasive physiologic support and drug removal, including partial exchange transfusion [79], plasma exchange [80], and hemofiltration with extracorporeal life support [81].

Consideration in Special Populations

Mitochondrial and Metabolic Disorders

Propofol exposure is associated with mitochondrial toxicity, myocyte apoptosis, and resulting muscular injury, even at low doses. Single doses of propofol have been reported to cause toxicity in patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), which may have been exacerbated by not providing a concomitant dextrose infusion [82]. Although there are also case series demonstrating some safe experiences using propofol in patients with mitochondrial disorders, patients with mitochondrial disorders are at overall increased risk of PRIS [83]. There are also reports of propofol unmasking mitochondrial disorders by causing toxicity in otherwise healthy patients who developed PRIS and were then found to have mitochondrial complex deficiencies [84]. Recommendations are that patients with known or suspected mitochondrial disorders should not receive prolonged or high-dose propofol for anesthesia or sedation [83].

Concern has also been raised whether patients with fatty acid oxidation disorders should receive propofol, due to risk that its lipid emulsion formulation could cause metabolic toxicity in these patients. For short-term (<1 hr) use in a series of patients with specific fatty acid oxidation disorders (long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency and trifunctional protein deficiency) undergoing sedated procedures, propofol accounted for only ~10% of their daily lipid intake limit and was not associated with any clinical side effects [39]. However, longer-term or higher-dose infusions will increase lipid exposure and toxicity in this patient population.

Conclusions

Propofol is an IV anesthetic drug with favorable short-term pharmacokinetics to provide rapid-onset, deep, and rapid-offset sedation. It results in dose-dependent CNS depression, hypotension, and respiratory depression; providers using propofol require experience and preparedness in airway management and advanced cardiorespiratory support. Long-term use is pharmacokinetically challenging, due to prolonged half-life with increasing infusion duration, and is not universally recognized as safe, due to the association between propofol infusion duration and mitochondrial toxicity (PRIS). In selected populations and for well-matched indications, propofol can be a useful sedation adjunct for the critically ill child.

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