Propofol Use in Children: Weighing the Benefit and Risk
Marcia L. Buck, Pharm.D., FCCP

P ropofol (2,6,-diisopropylphenol) has gained considerable favor as a sedative-hypnotic since its release in the United States in 1989. It offers the advantages of a quick onset of action, quick recovery once discontinued, and a low incidence of nausea and vomiting.[1] Although licensed by the Food and Drug Administration for use in children greater than 3 years of age only in the surgical setting, many pediatric practitioners have incorporated propofol into procedural sedation regimens and in the intensive care setting. This issue of *Pediatric Pharmacotherapy* will provide a brief review of propofol and the data published on its efficacy and safety in the pediatric population.

Efficacy in Children
Few drugs have been considered as controversial in the pediatric population as propofol. Since its release, a considerable body of literature, both supporting and discouraging its use, has been published. The efficacy of propofol as a sedative for children has been established in several clinical trials and case series.[2-9]

In one of the earlier papers, Borgeat and colleagues compared the efficacy of propofol to a combination of halothane and thiopental for short duration ear, nose, or throat surgery.[2] Forty children, aged 3-8 years, were randomized to receive 3mg/kg propofol followed by an infusion of 100 mcg/kg/min (6 mg/kg/hr) or 5-7 mg/kg thiopental with 0.5-1.5% halothane. Patient characteristics, as well as length and type of surgery, were not significantly different. Pain on injection and spontaneous movement were observed more frequently in the propofol group, while laryngospasm was seen more often in the thiopental group. Time to extubation as well as time to discharge were significantly shorter in the propofol group. More patients in the thiopental group required additional analgesics and

experienced nausea or vomiting. The authors concluded that propofol was appropriate as a single agent for short surgical procedures in children.

In that same year, Norreslet and Wahlgreen described the results of sedating three children in their intensive care unit with propofol during mechanical ventilation.[3] The doses used in these patients ranged from 23 to 50 mcg/kg/min (1-3 mg/kg/hr). All the children were adequately sedated, and no adverse effects were observed.

Among the largest series published to date in the intensive care setting are papers by Reed and colleagues.[6,7] In 1996, these investigators published a pharmacokinetically-based propofol dosing strategy developed in 29 children (<1 month to 15 years of age) receiving mechanical ventilation.[6] Patients were loaded with a dose of 2.5 mg/kg then immediately started on an infusion of 2.5 mg/kg/hr. The infusion was then titrated to maintain sedation for a 4 hour period. Based on their assessment of patient response, the authors suggest that beginning with high-dose therapy at 7.6 mg/kg/hr for the first hour then decreasing slowly to an average maintenance dose of 4.3 mg/kg/hr by the fourth hour is appropriate to maintain serum concentrations of 1 mg/L, which correlated with adequate sedation. In that same year, these authors also published a brief description of using propofol successfully in more than 140 children over a two year period of time, as part of another on-going clinical investigation.[7]

In 1999, two large-scale studies of procedural sedation with propofol were published. Havel, Strait, and Hennes conducted a prospective, blinded, randomized comparison trial of propofol versus midazolam in the emergency department of a tertiary care hospital.[8] Over a 14-month

period, 91 children between the ages of 2 and 18 were enrolled. Propofol was given as a 1 mg/kg bolus followed by an infusion of 67-100 mcg/kg/min (4-6 mg/kg/hr); midazolam was given as an initial dose of 0.1 mg/kg followed by dose increments of 0.05-0.1 mg/kg as needed. Propofol was found to provide a similar degree of sedation to midazolam, with a shorter recovery time (mean $\pm$SD of 14.9$\pm$11.1 versus 76.4$\pm$47.5 minutes). The most frequently observed adverse effect was mild, transient hypoxemia, occurring in approximately 10% of patients in both groups. The authors concluded that propofol appears to be a useful tool for sedation in the emergency department.

Hertzog and coworkers performed a retrospective review of propofol use during invasive procedures in their intensive care setting.[9] During a 20-month period, 115 children (average age 6.4 years) were treated during 251 procedures. The mean dose used for induction was 1.8 mg/kg with a mean total dose of 8.8 mg/kg. In 13% of the cases, midazolam was also given. The average induction time was 3.9 minutes, and recovery time was 28.8 minutes. All the patients achieved adequate sedation. Of the 251 procedures, 98% were completed successfully. Transient hypotension occurred in 50% of the patients but did not significantly alter perfusion. Respiratory depression occurred in 6% of cases and transient myoclonus in 3.6%.

Pharmacokinetics
Following intravenous administration, propofol serum concentrations fall rapidly as the drug is widely distributed into the tissues. The volume of distribution of propofol in adults is estimated to be approximately 2-5 L/kg after a single dose and 25-60 L/kg after continuous administration over a week. It is highly protein bound (96-99%). Propofol is metabolized by conjugation into several inactive metabolites, which are then renally eliminated. Approximately 50% of a dose is converted to a glucuronide conjugate. Clearance from the central compartment is rapid, with values in adults ranging from 23-50 ml/kg/min. The terminal elimination half-life of propofol in adults is typically between 1 to 3 days after continuous administration, reflecting the extensive distribution into tissues and slow reaccumulation in the serum.[1,10]

The pharmacokinetic profile of propofol in children after a single dose has been described in several studies. Jones et al reported the results of administering a single 2.5 mg/kg propofol dose

to 12 children, ages 4-12 years, during surgery.[11] Mean (SEM) apparent volume of distribution in this study was 5.0 (2.7) L/kg, with a total body clearance of 40.4 (3.6) ml/min/kg, and an elimination half-life of 209 (29) minutes. In a study of 12 children ages 1-3 years given a single dose of 4 mg/kg, Murat and coworkers reported an average volume of distribution of 9.5$\pm$3.7 L/kg with an average total body clearance of 53$\pm$13 ml/min/kg.[12] Not unexpectedly, younger children demonstrated a larger volume of distribution, with a similar rate of clearance.

Reed and colleagues reported the pharmacokinetic parameters obtained in 19 children participating in the propofol dose titration study described earlier.[6] After repeated dosing in an intensive care unit environment, average propofol pharmacokinetic parameters were as follows: volume of distribution 15.1$\pm$5.5 L/kg, total body clearance 49.6$\pm$9.1 ml/min/kg, and half-life 9.8$\pm$2.1 hours.

Adverse Effects
Transient pain at the site of injection is reported in approximately 10-20% of patients given propofol. This may be reduced by the concomitant use of lidocaine (0.5-1 ml of a 1 or 2% solution). Phlebitis and thrombosis associated with propofol are rare, occurring in less than 1% of patients treated.[1,10]

Other common adverse effects associated with propofol use include: hypotension and bradycardia (3-10% of adults studied during surgery, 26% of adults studied in intensive care, and 17% of children), excitatory movement and myoclonus (3-10% in adults; 17% in children), rash (1-5%), apnea (1-3%), and hyperlipidemia with long-term use (3-10%).[1,10] Patients with known seizure disorders and those with lipid metabolism disorders may be at increased risk for adverse effects.

Respiratory acidosis has been reported in up to 10% of patients (adults and children) during clinical trials and in several case reports.[1,10] In many of these cases, this reaction has occurred while the patient was being weaned from the ventilator in anticipation of extubation.

Of greatest concern for pediatric practitioners are the case reports of fatal metabolic acidosis and cardiac failure, termed the propofol-infusion syndrome, that have been reported in over a dozen children.[13-19] In 1992, Parke and colleagues at the John Radcliffe Hospital in

Oxford reported five cases involving a possible link to propofol.[13] The children, between 1 month and 6 years of age, were all sedated during intubation for acute respiratory tract infections. Propofol doses ranged from 4 to 10 mg/kg/hr (average rate 8.2 mg/kg/hr). Total infusion time ranged from 66 to 115 hours. In each of the cases, the patients developed metabolic acidosis after 24 hours of more of propofol and progressed to multiorgan failure, refractory bradycardia, and asystole.

While the mechanism for this reaction is still unclear, it should be noted that in all five cases the patients were also lipemic, possibly indicating an inability to clear the large amounts of drug. Several additional cases have subsequently been published describing metabolic acidosis with or without lipemia occurring with propofol use in children.[14-18]

In contrast to these cases, other investigators have published large patient series and clinical trials in which this reaction was not observed. The experience of Reed and colleagues has been described earlier.[4,5] In 1997, Pepperman and Macrae conducted a retrospective study comparing the results of 106 critically ill children who had received propofol and 92 who were given midazolam.[20] They observed no difference in the number of patients who developed metabolic acidosis or other complications from their sedative therapy.

In a 1992 review, the Food and Drug Administration concluded that propofol had not been shown to have a direct link to any pediatric deaths.[21] While the causal relationship between propofol and metabolic acidosis remains unproven, clinicians should be aware of the risk for this reaction in children and limit the dose and duration of propofol therapy accordingly. Some authors have suggested that monitoring for lipemia or hypertriglyceridemia during therapy should also be considered as an indication of propofol accumulation.

Other rare reactions linked to propofol use include anaphylaxis and anaphylactoid reactions, premature atrial contractions, dystonia or paresthesia, hypersalivation, wheezing, flushing, amblyopia, or discoloration of the urine.[1,10] In addition to these adverse effects, some patients have experienced a withdrawal syndrome consisting of restlessness, jitteriness, myoclonus, or seizures up to two weeks after discontinuing propofol.[1,22]

Dosing Recommendations

Propofol is available as Diprivan® (Zeneca) in 20 ml ampules as well as 50 and 100 ml vials and 50 ml prefilled syringes. The preparation is an oil-in-water emulsion which contains 100 mg/ml soybean oil, 22.5 mg/ml glycerol, and 12 mg/ml egg lecithin. Each ml of propofol provides 0.1 g of fat (1.1 kcal). The emulsion may be given undiluted, or diluted with 5% dextrose to a concentration less than 2 mg/ml.[10] Propofol is now also available as a generic by Baxter.

Because of the ability of propofol to serve as a growth medium for microorganisms, vials are designed for single use. While they contain either disodium edetate or sodium metabisulfite to retard the growth of microbes, it is still possible to contaminate the emulsion. Aseptic technique must be used during preparation, and vials should be discarded within 12 hours of opening. It is recommended that once propofol is diluted and/or transferred to an alternative delivery system, such as a syringe, it should be discarded within 6 hours. Intravenous tubing should be changed every 12 hours during continuous infusion of propofol.[10]

For induction of anesthesia, an intravenous dose of 2.5-3.5 mg/kg administered over 20-30 seconds is recommended for children. More rapid administration of propofol is associated with a greater risk for hypotension. The induction dose may be followed by an infusion of 7.5-18 mg/kg/hr (125-300 mcg/kg/min) for maintenance of general anesthesia.[10] In the intensive care setting, lower doses of 1-4 mg/kg/hr should be used, with titration to the desired response.[3,6]

Summary

Propofol is a useful agent for sedation in children undergoing surgery or medical procedures, and for short-term use in the intensive care unit. It offers the advantage of a short duration of action allowing rapid dose titration and reversal, and is generally well tolerated. The potential association between propofol use and metabolic acidosis, however, must be considered when using this agent in the pediatric patient population.

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Literature Review

Hypertension management review

This concise review describes therapies currently in use to treat hypertension in the neonatal and pediatric population. The authors discuss both nonpharmacologic and pharmacologic treatment strategies, with emphasis on the most commonly prescribed antihypertensives by therapeutic class. Table 2 is a particularly useful compilation of drug dosages that alone makes this article a valuable addition to the files of any pediatric health care professional. Temple ME, Nahata MC. Treatment of pediatric hypertension. **Pharmacotherapy 2000;20:140-50.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 4/28/00:

1. A second synthetic volume expander (Hextend®) was added to the Formulary in an effort to reduce the use of albumin.

2. Rapacuronium (Raplon®), a short-acting nondepolarizing neuromuscular blocker, was also added. This agent is designed for use during intubation or short procedures and is restricted to use in the OR and VASC. The usual dose in pediatric patients is 2 mg/kg given intravenously.

3. As part of a class review of angiotensin inhibitors, ramipril (Altace®) was added to the Formulary and fosinopril (Monopril®) was removed. Trandolapril (Mavik®), moexipril (Univasc®), and perindopril (Aceon®) were rejected. The consideration of quinapril (Accupril®) was tabled.

4. Dofetilide (Tikosyn®) was added to the Formulary for the conversion and management of recurrent atrial fibrillation/atrial flutter.

5. Fenoldopam (Corlopam®) was added to the Formulary for the short-term management of severe hypertension. It is a rapid-acting vasodilator with activity at dopamine and alpha-adrenergic receptors. Its use is restricted to the CCU, TCVPO, and OR.

6. Linezolid (Zyvox®), an oxazolidinone antibiotic used for the management of patients with methicillin and vancomycin-resistant infections, was given provisional approval.