Survey of Pharmacists Regarding the Use of Propofol Infusions in the PICUs in North America

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OBJECTIVE The objective of this survey was to assess the current use of continuous infusion propofol in PICUs across the United States and Canada.

METHODS A list of institutions with PICU beds/units was identified through the residency directories available on the American Society of Health-Systems Pharmacists (ASHP) and Canadian Society of Hospital Pharmacists (CHSP) Web sites. A REDCap questionnaire was sent to each identified institution's program director via email. An initial reminder email was sent out 2 weeks later and a second reminder email was sent 4 weeks after the initial request. The survey was closed at 6 weeks.

RESULTS A total of 514 emails were sent to residency program directors, and 50 pharmacists responded to the survey. Of the pharmacists that did respond, 27 (54%) reported using propofol while 23 (46%) did not. Of those that did not, 43.5% reported the FDA boxed warning as the primary reason. Thirty-seven percent of respondents using propofol felt comfortable using a maximum infusion rate of 200 mcg/kg/min. Twenty-nine percent, 25%, and 33% of those who responded as using propofol felt comfortable using this agent for a maximum duration of 24, 48, and 72 hours, respectively. The majority of respondents using propofol did not have a case of propofol-related infusion syndrome.

CONCLUSIONS Despite the FDA warning, propofol is used as a continuous infusion (with variable limitations) by a majority of pharmacists in North America. Self-reported incidence of propofol-related infusion syndrome (PRIS) remains low.

ABBREVIATIONS ASHP, American Society of Health-Systems Pharmacists; CSHP, Canadian Society of Hospital Pharmacists; PICU, pediatric intensive care unit; PRIS, propofol-related infusion syndrome

KEYWORDS adverse drug effect; continuous infusion; pediatrics; propofol; propofol-related infusion syndrome

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Introduction

Propofol is a short-acting anesthetic agent that is unlike other sedatives available. Its duration of action is roughly 10 minutes, making it useful in a variety of different settings. Propofol is commonly used as a sedating agent in adult ICUs.¹ In 2001, the FDA warned that propofol was not indicated for use in children < 16 years old after several pediatric deaths were attributed to propofol-related infusion syndrome (PRIS).^{1,2} After the FDA warning regarding PRIS,³ propofol use in PICUs fell out of favor.

PRIS was first identified in 1992 after a case series discussed 5 patients in a PICU who received high doses and prolonged duration of continuous propofol infusions.^{4,5} Following this case series, roughly 80 deaths were attributed to PRIS.^{2,6–11} Common symptoms attributed to PRIS include metabolic acidosis (20%–86%), cardiac dysfunction (43.7%–88%), hypotension (34%–62%), rhabdomyolysis (27%–52%), hepatic failure (24%), hypoxia (17.5%), and hypertriglyceridemia

(5.3%–15%).^{12–14} These symptoms are believed to be caused by a propofol-derived impairment within the electron transport chain that results in elevated levels of malonylcarnitines and acylcarnitines during propofol administration.^{15,16} This creates the subsequent sequelae associated with PRIS.

PRIS is associated with doses higher than 83 mcg/kg/min, infusion duration greater than 48 hours, and pediatric patients.¹⁷ The concern for PRIS, coupled with the FDA warning, prompted many institutions, including our own, to avoid continuous propofol infusions in pediatric patients. Despite the FDA warning, it is believed that propofol can be safely used in the pediatric population. A retrospective case series by Cornfield et al¹⁸ reviewed 142 patients who received continuous infusion propofol. The maximum dose was 50 mcg/kg/min with an option for a 1-mg/kg bolus once per hour. Most patients received continuous infusion propofol for <48 hours. No instances of metabolic disturbances or hemodynamic instability were seen. This study suggests that using lower doses and a shorter duration can mitigate the

Table 1. Pharmacist and Institutional Demographic Data

Category	Option	Response, No. (%)
Years of practice	Resident	2 (4)
	0–5	7 (14)
	5–10	15 (30)
	10–20	16 (32)
	>20	10 (20)
Average number of patients admitted to the PICU/yr	<250	15 (31)
	250–600	10 (20)
	601–1000	10 (20)
	1001–1500	2 (4)
	>1500	11 (22.9)
PRIS cases	None	36 (73)
	<3	11 (22)
	3–5	2 (4)
	6–10	0
	>11	0
Use of continuous infusion propofol in PICU	Yes	27 (54)
	No	23 (46)
Number of patients prescribed continuous infusion propofol/mo	1–5	21 (80)
	5–10	2 (7)
	10–20	3 (11)
Written policy regarding continuous infusion propofol use	Yes	26
	No	74
Reasons for not using continuous infusion propofol	FDA boxed warning	10 (43.4)
	Institutional policy	3 (13)
	Personally uncomfortable	2 (8)
	Other	8 (34)

PRIS, propofol-related infusion syndrome

risk of PRIS when using continuous infusion propofol. Studies such as this have produced a growing interest into the reintroduction of continuous infusion propofol into practice in PICUs.

This has led to wide variations in practice, as some institutions provide propofol infusions and others maintain their avoidance of the agent. Therefore, the purpose of this study was to assess the use of propofol in PICUs across the United States and Canada. Additional aims were to describe continuous infusion propofol prescribing practices, institutional safety practices, and the subsequent incidence of PRIS.

Materials and Methods

This study was a survey of propofol use practices in PICUs in the United States and Canada. This survey was deemed to be exempt by the Institutional Review Board at the University of Illinois College of Medicine at Peoria. A list of institutions with pediatric beds/units was identified through the residency directories available on the American Society of Health-Systems Pharmacists (ASHP) and Canadian Society of Hospital Pharmacists (CHSP) Web sites. The email address of each pharmacy director with a pediatric unit and/or pediatric beds was then used to contact the program.

A questionnaire via REDCap¹⁹ (Vanderbilt University, Nashville, TN) was sent to each identified institution via email with a cover letter in order to indicate to the designated pharmacist that this was a research endeavor. The cover letter suggested that the program directors complete or forward the survey to applicable personnel with experience in pediatric critical care. The first email was sent January 1, 2017. The first reminder email was sent 2 weeks later and a second reminder email was sent 4 weeks after the initial request. The survey was closed at 6 weeks.

Components of the survey included country of practice, years of PICU practice, and average yearly number of PICU admissions. If propofol was used by the institution, the following information was collected: 1) number of patients per month given continuous infusion propofol; 2) indications for propofol use; 3) use of a written protocol in regard to maximum dose and/or duration of continuous infusion propofol; 4) maximum dose and duration of continuous infusion propofol; 5) contraindications to propofol usage; and 6) number of cases of PRIS encountered (Table S1). The survey was set up in such a way that if a respondent answered “Yes” to question No. 5 “Do you (or your institution) use continuous infusion propofol in your PICU?” questions 6

Table 2. Maximum Dose and Duration of Propofol Use in the PICU

Propofol Dosage Information	Number of Respondents (%)
Maximal Dose (mcg/kg/min)	
<50	2 (7)
100	8 (29)
150	6 (22)
200	10 (37)
No maximum dose	5 (3)
Maximal Duration (hr)	
<12	3 (11)
24	8 (29)
48	7 (25)
72	9 (33)
No maximum duration	0 (0)

to 12 would then populate to be answered. The survey would end if the respondent answered “No” to question No. 5 to prevent the respondent from having to answer questions that were not applicable.

Descriptive statistical methods were used to summarize data and provide a description of responses. Frequencies, percentages, and mode were reported for categorical variables. The Fischer exact test was used to compare categorical variables when indicated. A p value ≤ 0.05 was considered statistically significant. All statistical analyses were performed by using JMP software V 12 (SAS Institute Inc, Cary, NC).

Results

The survey was sent to 514 residency program directors identified as having a pediatric service. Fifty pharmacists from different institutions responded to the survey, 48 from the United States and 2 from Canada, for a response rate of 9.7%. Survey respondents had varied years of experience in the PICU with 62% between 5 to 20 years of experience and 20% with >20 years of experience. The volume of patients seen in PICUs also varied with 31% reporting <250 admissions/year and 23% with >1500 admissions/year.

Of the 50 respondents, 54% reported using propofol as continuous infusion in the PICU, with 80% reporting use on 1 to 5 patients/mo and 11%, >10 patients/mo. Only 26% of all reporting institutions had a written policy regarding propofol use in their unit. Despite frequent use of propofol in the PICU, 73% of the pharmacists had not observed any case of PRIS in their practice. Of 10 pharmacists with >20 years of practice, 80% had not witnessed any cases of PRIS. Of the 23 respondents who did not use propofol as a continuous infusion, the majority (43%) did not do so owing to a FDA boxed warn-

Table 3. Indication for Use of Propofol Infusion in PICU and Number of Respondents Using Propofol Infusion for Each Indication

Indication	Use, n (%)
Short postoperative sedation	16 (32)
Difficult sedation	16 (32)
Difficult extubation	14 (28)
Patient transport/transfer	3 (6)
Weaning from other sedating agents	16 (32)
Control of intracranial pressure	7 (14)
Status asthmaticus	1 (2)
Status epilepticus	10 (20)

ing (Table 1). No significant difference was observed between respondents using higher doses and longer duration with self-reported experience with incidence of PRIS at their institution.

As compared with smaller units (<1000 admissions/yr), larger units tend to use propofol more often (85% compared with 43%, $p = 0.02$). Almost all respondents who used propofol have restrictions on the maximum dose or duration of propofol infusion. Thirty-seven percent were comfortable with a maximum dose of 200 mcg/kg/min and 33% were comfortable with a maximum duration of 72 hours. Only 3% reported no maximum dose and no respondents use propofol with no restriction on duration (Table 2).

Propofol was used for a wide variety of indications. Short postoperative sedation, difficult sedation, and weaning from other sedative agents were the most frequent indications for use (59%). Patient transfer/transport (11%) and status asthmaticus (3%) were the least popular indications (Table 3). Most respondents (82%) considered some aspects of patient characteristics as an absolute contraindication of use of propofol in the PICU (Table 4). The specific factor varied, with duration of use >72 hours and presence of inborn errors of metabolism considered as contraindications by the highest proportion of respondents (26%). No pharmacist considered use of total parenteral nutrition (i.e., lipid emulsion) or presence of neurodegenerative disease as an absolute contraindication for the use of propofol infusion.

Discussion

It is often a challenge to maintain adequate control of pain and sedation in the pediatric patient given the wide variation in pharmacokinetics throughout childhood. This has become more difficult recently as medications are removed from the market, institutions experience drug shortages, or additional deleterious adverse events are described. Propofol offers an additional modality to provide adequate sedation control; however, the concern for PRIS and subsequent FDA

Table 4. Potential Absolute Contraindications for the Use of Continuous Infusion Propofol in the PICU

Potential Absolute Contraindications	Yes*, n (%)	No†, n (%)
<1 yr age	7 (14)	43 (86)
Duration >72 hr	13 (26)	37 (74)
Myocardial dysfunction	8 (16)	42 (84)
Total parenteral nutrition	0	50(100)
Neurodegenerative disease	0	50 (100)
Inborn errors of metabolism	13 (26)	37 (74)

* Respondents who consider condition to be an absolute contraindication to use of propofol infusion.

† Respondents who do not consider the condition to be an absolute contraindication to use of propofol infusion.

warning has resulted in an avoidance of this medication in pediatrics. After the FDA warning, a few studies were conducted using this agent in the pediatric population.

A national survey by Kruessell et al¹⁷ showed that propofol was being used in PICUs in Germany. Most users of continuous infusion propofol followed tightly controlled regimens, with dose limits ≤ 4 mg/kg/hr (66.67 mcg/kg/min) and a maximum duration of use of 48 hours.¹⁶ A contrasting study out of Great Britain by Hill et al²⁰ illustrated the wide variation in propofol use among the 242 responding institutions; 172 respondents rarely or never used the agent, while 62 respondents used continuous propofol infusions on a monthly basis. The majority of these respondents did not state a maximum dose (79%) or duration of use (54%). This survey concluded that more studies are needed to facilitate the knowledge of the underlying mechanisms of PRIS in its relation to propofol usage with further data regarding a maximum duration and dose to ensure safe and appropriate use of propofol in the pediatric population.

Continuous infusion propofol would then provide an alternative medication for sedation, as there are limited options. Midazolam is a commonly used sedative agent, yet has been shown to alter hippocampal growth and neurodevelopmental outcomes. In a study by Duerden et al,²¹ the analgesic-sedative exposure on hippocampal growth was assessed in preterm infants, as was that of hippocampal growth on neurodevelopmental outcome. The authors concluded that midazolam exposure was associated with macrostructural and microstructural alterations in hippocampal development and poorer outcomes consistent with a disruption in hippocampal maturation in this patient population. The hippocampus plays an important role in memory and cognition. Therefore, medications such as midazolam that impair hippocampal growth can result in long-term negative neurologic outcomes. Ketamine, another common sedative used in pediatric patients, has also been shown to alter neurodevelopmental outcomes in animal studies. Neuronal calcium oscillations are present in the immature brain, during a period of high plasticity, and regulate neuronal differentiation and synaptogenesis.

These oscillations are mediated by glutamate in astrocytes.²¹ By blocking glutamine via the NMDA receptor, it is proposed that ketamine exerts its toxic effect through the suppression of neuronal calcium oscillations, leading to reduced synaptic integrity and impaired synaptogenesis.²³ Simply, ketamine prevents communication from synapses to neurons and can negatively impair neurologic functions such as memory and learning.

Propofol on the other hand has neuroprotective properties, which would make this agent potentially preferred over other sedating agents in terms of better long-term neurodevelopmental outcomes. It acts as a neuroprotective agent through the activation of gamma-aminobutyric acid receptors, thereby modulating the excitatory amino acid transmitter system and protecting brain cells against oxidative stress.²⁴ Propofol also suppresses apoptosis and inflammation, enhancing its neuroprotective effects on the developing brain.²⁵ Dexmedetomidine is a newer sedative agent and has gained popularity with its potential neuroprotective effects.^{25,26} Dexmedetomidine's half-life and side effect profile preclude its use in certain settings such as the patient who needs frequent neurologic checks or those with cardiovascular instability. Thus, sedation agents may be limited in certain clinical scenarios.

It has also been shown that both opioids and benzodiazepines may increase the incidence of delirium among PICU patients exposed to these agents, ultimately leading to an increased length of stay as shown by Smith et al.²⁷ An increase in delirium was associated with higher rates of benzodiazepine exposure in this study. Continuous infusion propofol may allow for a reduction in benzodiazepine exposure, helping to align with The Pain Agitation Delirium guidelines set forth by the Society of Critical Care Medicine, which stresses the importance of limiting sedative exposure in children.²⁸

One major limitation to this survey is the response rate. A total of 514 emails were obtained from ASHP and CHSP Web sites, yet only 50 responses were received. The response rate of 9.7% is very low as compared with other surveys regarding this topic, which generally had a 50% to 60% response rate. The 514 institutions were selected owing to a description on the ASHP

or CHSP Web site stating a pediatric population was served. This method was used to try to maximize the number of responses received and to not solely focus on large pediatric institutions. Thus, not all of the selected institutions may have had someone with PICU experience, in which case, the response rate could be higher than 9.7%.

The results of this survey are similar to those conducted elsewhere and illustrate the continued variation in practice among institutions regarding the use of continuous infusion propofol. The respondents were mixed in the use of propofol in the pediatric population. Despite the FDA boxed warning, 54% of respondents reporting using propofol with 37% of these respondents using doses as high as 200 mcg/kg/min.

Conclusions

The results of our survey suggest that there is a wide variation of practice regarding the use of continuous propofol infusions in pediatrics. Propofol is used for certain indications, such as short postoperative sedation, difficult sedation, and weaning from other sedative agents. Despite low rates of PRIS, monitoring should continue to avoid this potential adverse effect.

ARTICLE INFORMATION

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Supplemental Material

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