Is Propofol a Friend or a Foe of the Pediatric Intensivist? Description of Propofol Use in a PICU*

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Objective: The primary objective is to describe the practice patterns of nonprocedural propofol use in a single-center referral PICU. The secondary objective is to describe the rate of concordance of propofol use with the PICU local practice of a maximum mean rate of 4 mg/kg/hr and a maximum duration of 24 hours and to assess for signs and symptoms of propofol infusion syndrome.

Design: Retrospective descriptive cohort study.

Setting: PICU of a tertiary care teaching hospital and referral hospital for the Western Canada.

Patients: Children 1 month to 17 years old who received a nonprocedural propofol infusion between January 1, 2009, and December 31, 2009.

Interventions: None.

Measurements and Main Results: Two hundred twenty-three infusions (representing 210 unique patients) were included in the study. The median average infusion rate (interquartile range) including boluses was 2.7 mg/kg/hr (1.9–3.6 mg/kg/hr), and the mean infusion duration (SD) was 10.3 hours (6.7 hr). Eighty-seven percent and 98% of infusions were concordant with PICU intensivists self-reported practice maximum rate and duration, respectively. No cases of propofol-related infusion syndrome or deaths associated with propofol infusions were identified.

Conclusions: The use of propofol infusions was in concordance with PICU local practice, and propofol infusion syndrome did not developed in patients. In agreement with previous recommendations, propofol infusions in the PICU appear to be safe when limiting doses to 4 mg/kg/hr and for less than 24 hours; however, appropriate monitoring of adverse effects is still warranted due to absence of robust evidence. (*Pediatr Crit Care Med* 2014; 15:e66–e71)

Key Words: critical care; pediatric intensive care unit; propofol; propofol infusion syndrome

Adequate sedation is an important part of care for critically ill patients to reduce discomfort and anxiety and to improve tolerance of various procedures and treatments, including mechanical ventilation. Propofol is an alkylphenol IV sedative-hypnotic agent. With its rapid onset (approximately 10–50 s) and short duration of action (approximately 3–10 min) (1, 2), propofol has become a popular sedative choice in critically ill patients due to its rapid induction of anesthesia, more sensitive titration of sedation level, and fast recovery on discontinuation (3, 4). However, propofol is not without adverse effects, such as pain on injection, apnea, and hypotension (1, 2, 5). One serious adverse event is propofol-related infusion syndrome or propofol infusion syndrome (PRIS), a constellation of signs and symptoms, including bradycardia, metabolic acidosis, liver enlargement, lipemic plasma, rhabdomyolysis and/or myoglobinuria, and even death. PRIS was first described by Bray (6) in a retrospective review of critically ill children in which he proposed that the risk was greater in those receiving mean doses more than 4 mg/kg/hr for more than 48 hours. In 2002, Health Canada issued a notice that propofol was contraindicated for sedation in pediatric patients receiving intensive care (7). Despite these concerns of PRIS, propofol continues to be used, largely because of its favorable pharmacokinetic profile.

The Stollery Children's Hospital PICU continues to use propofol primarily to facilitate weaning of longer acting sedatives around a planned extubation. The primary objective of this study was to describe the practice patterns of propofol use in a tertiary care PICU. The secondary objectives were to describe the rate of concordance of propofol use with

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this local practice and to assess for the presence of signs and symptoms of PRIS.

MATERIALS AND METHODS

This descriptive retrospective cohort study involved patients admitted to the Stollery Children's Hospital PICU in Edmonton, Alberta. The 19-bed Stollery PICU is a level 1 trauma center and is a referral center for solid-organ transplant, the surgical center for the Western Canadian Heart Network, and the North American reference center for Berlin Heart implantation.

In our PICU, propofol is titrated between 0 and 4 mg/kg/hr by the bedside nurses to achieve adequate sedation (by clinical examination). It is discontinued after a successful pressure support trial, prior to extubation. Once on the propofol infusion, all other lipid infusions are stopped. Our local practice is to run a maximum infusion rate of 4 mg/kg/hr (plus up to 1 mg/kg/hr as needed boluses) for a maximum of 24 hours.

Patient Eligibility

Pediatric patients admitted to the PICU were eligible for inclusion if they had received a continuous propofol infusion for nonprocedural sedation between January 1, 2009, and December 31, 2009. For patients receiving a propofol infusion on more than one occasion during their PICU stay, only the first infusion per admission was included. The study exclusion criteria were the following: propofol infusions outside the PICU (operating room, emergency department, and/or transport) and unplanned extubation while on the propofol infusion. We also excluded from the PRIS analysis those patients who had clinical or laboratory signs that could mimic PRIS at admission to the PICU or in whom these signs developed 12 hours prior to receiving the propofol infusion.

Data Collection

Patients were identified through a pharmacy dispensing database, and data were collected retrospectively from the patient's chart. Data collection included demographics, admission diagnosis, propofol infusion rates and bolus doses, infusion duration, mechanical ventilation, and concurrent use of other analgesic and sedative medications. The average propofol infusion rate was calculated by dividing the total amount of propofol (mg/kg) received by the total duration of the infusion (hours). The total propofol dose (mg/kg/hr) was calculated by adding the propofol bolus doses (mg/kg) received during the infusion to the average infusion rate calculation. To address the safety of propofol infusions in PICU, we also collected the following variables: heart rate at baseline (before the infusion was started), the heart rate at the end of the infusion, the percentage of the heart rate variation between those two time points, the need for fluid resuscitation, the initiation or increase in inotropic/vasopressor support, and the occurrence of a lactic acidosis (lactic acid level > 2.2 mmol/L) during the propofol infusion.

Although different definitions of PRIS and different criteria for its diagnosis exist, for the purposes of this study, the definition by Bray (6) was used, as it was developed based on a retrospective review in PICU patients. PRIS was defined as "[a] the sudden, or relatively sudden, onset of a marked bradycardia which was resistant to treatment and which progressed to asystole; [b] the presence of lipemic plasma; [c] a clinically enlarged liver or one which was found to be infiltrated with fat at autopsy; [d] the presence of a metabolic acidosis to the extent of at least one arterial blood sample with a base deficit greater than 10 mEq/L; [e] the presence of muscle involvement with evidence of rhabdomyolysis or myoglobinuria." A diagnosis for PRIS required the presence of [a] and at least one of [b], [c], [d], or [e] (6). The following definitions were used to establish the presence or absence of sign and symptoms compatible with PRIS: bradycardia as a heart rate measurement of less than 60 beats/min with signs of hemodynamic instability necessitating chest compressions and/or use of chronotropic drugs (such as epinephrine or atropine) (8); lipemic plasma as a serum triglyceride more than 2.3 mmol/L (9); metabolic acidosis as at least one arterial blood gas measurement with a base deficit more than 10 mEq/L (6); rhabdomyolysis as creatine kinase values above normal ranges as reported by our local laboratory and with an increasing trend in values (10); and myoglobinuria as urine myoglobin values above normal as reported by our local laboratory (11). Information related to signs and symptoms of PRIS was collected at admission and between 12 hours before and 72 hours after the discontinuation of the propofol infusion as described in previous studies (12). Extubation failure was defined as reintubation within 24 hours.

This study was approved by the University of Alberta Health Research Ethics Board.

Data Analysis

Patient demographic and propofol infusion characteristics were summarized as descriptive statistics. The data were reported as absolute numbers, proportions with 95% CIs, means with SD, or medians with interquartile range (IQR), as appropriate. Data were analyzed using the statistical data analysis package, STATA (StataCorp 2007, Stata Statistical Software: Release 10; StataCorp LP, College Station, TX).

RESULTS

Data were collected from 210 patients who received a total of 223 propofol infusions. The median (IQR) age of the patients in the sample was 1.2 years (0.5–5.7 yr), and 118 were male (53%). The median (IQR) weight was 9.6 kg (6–20) (**Table 1**). About half were patients admitted for cardiac reasons (majority of which were postcardiac surgery), followed by those admitted for respiratory reasons (majority of which were respiratory distress due to viral or bacterial infections and postrespiratory operations or procedures).

Patterns of Propofol Use

The median (IQR) propofol dose, not including the bolus doses, was 2.4 mg/kg/hr (1.8–3.1 mg/kg/hr). When bolus doses were included, the median (IQR) propofol dose was 2.7 mg/kg/hr (1.9–3.6 mg/kg/hr) (**Fig. 1**). By including the bolus doses, the number of infusions greater than the local policy of 4 mg/kg/hr increased from 11 (5%; 95% CI, 2–9) to 30 (13%; 95% CI, 9–19). This resulted in an 87% concordance

TABLE 1. Baseline Patient Characteristics

Characteristic	Median (IQR)
Age (yr)	1.2 (0.5–5.7)
Males	118 (53)
Weight (kg)	9.6 (6–20)
Reason for admission	*n* (%)
Cardiac	106 (48)
Respiratory	50 (22)
Neurologic	30 (13)
Sepsis	6 (3)
Other	31 (14)

IQR = interquartile range.

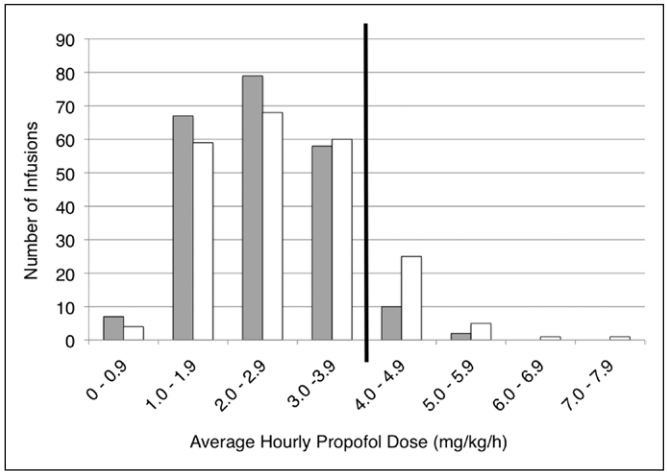

Figure 1. Median average hourly propofol dose in PICU patients, without propofol bolus doses (*gray bars*) and with bolus doses (*white bars*). *Black line* indicates the physicians' self-reported practice of 4 mg/kg/hr maximum infusion rate.

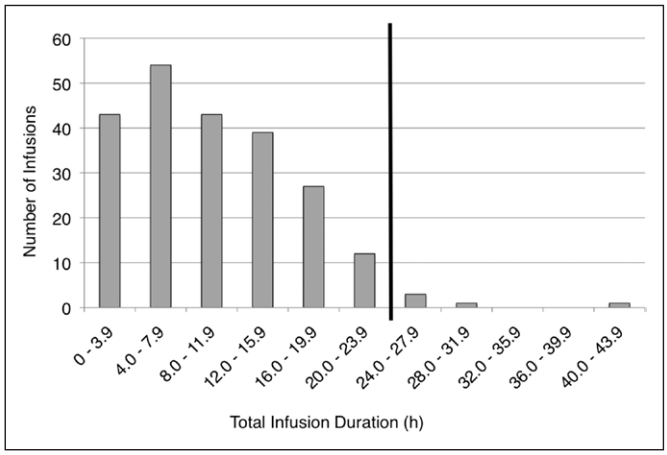

Figure 2. Total infusion durations of propofol infusions in PICU patients. *Black line* indicates the physicians' self-reported practice of maximum infusion duration of 24 hr.

rate with the policy, when the boluses were included. The minimum and maximum infusion rates (including bolus doses) were 0.5 and 7.8 mg/kg/hr, respectively.

The mean (SD) infusion duration was 10.3 hours (6.7 hr) with a minimum duration of 0.3 hours and maximum of 41.3 hours. The majority of the infusions (98%) were less than 24 hours (**Fig. 2**).

The mean (SD) cumulative dose for the sample was 29.2 mg/kg (24.1 mg/kg). One hundred sixty infusions (72%; 95% CI, 65–77) were accompanied by at least one propofol bolus dose, and 188 infusions (84%; 95% CI, 78–88) were given with a concurrent analgesic and/or sedative. The most common analgesic/sedative used with propofol was morphine (76%; 95% CI, 69–82) followed by a combination of opioids (morphine or hydromorphone) and midazolam (9%; 95% CI, 5–14), fentanyl alone (7%; 95% CI, 4–11), hydromorphone alone (6%; 95% CI, 3–10), and midazolam alone (2%; 95% CI, 1–4). Of the 223 included propofol infusions, 168 infusions (75%; 95% CI, 69–80) were associated with successful extubations, 33 (15%; 95% CI, 10–20) with postponed extubations due to respiratory reasons (i.e., increased work of breathing, desaturations, changes on chest radiography, and lack of cuff leak/cough/gag), seven (3%; 95% CI, 1–6) with reintubations within 24 hours, and one infusion (0.4%; 95% CI, 0–2) was discontinued due to a decision to extubate and withdraw life-sustaining therapy. All patients who required reintubation within 24 hours had respiratory distress, not over sedation. Of the remaining instances where patients were still intubated when propofol was discontinued, three (1.3%; 95% CI, 0–4) were due to adverse drug effects, one (0.4%; 95% CI, 0–4) was due to ineffectiveness at lowering intracranial pressure, seven (3%; 95% CI, 1–6) were to facilitate neurologic assessment in patients with CNS injury, and three (1.3%; 95% CI, 0–4) were for unknown reasons.

On average, the heart rate changed by 2% while on propofol infusion, and none of these patients needed interventions to increase their heart rate. Three patients (1%; 95% CI, 1–6) were started on inotropic support while on the propofol infusion; these patients were in the postoperative period after surgical repair of congenital heart disease and remained on inotropes after propofol was discontinued. None of the patients who were already on inotropic support had their dose increased during the propofol infusion. Twelve children (5%; 95% CI, 3–9) received a fluid bolus for low blood pressure during the propofol infusion, and mean (SD) dose received was 8.8 mL/kg (5.1 mL/kg). Only four patients (2%; 95% CI, 0–4) had lactic acidosis while on propofol, three children already had a lactate level more than 2.2 mmol/L when propofol was started and the acidosis resolved after the infusion, and lactic acidosis developed in one patient while on propofol (lactic acid level 2.5 mmol/L).

Adverse Events and Presence of PRIS

One hundred ninety-four patients (92%; 95% CI, 85–95) had none of the signs and symptoms that are used in the diagnostic criteria for PRIS in the 12 hours preceding propofol infusion and were therefore included in this analysis. Lipemic plasma developed in four of these patients (2%; 95% CI, 0–5), and mild metabolic acidosis (pH 7.20–7.30) developed

in four patients (2%; 95% CI, 0–5) while on the propofol infusion. In all cases, these symptoms resolved spontaneously without any intervention. None of the patients were diagnosed with significant myoglobinuria, rhabdomyolysis, and/or hepatomegaly. More important, according to the criteria by Bray (6) , the diagnosis of PRIS requires the development of bradycardia/asystole; therefore, based on this definition, we did not find PRIS in any patients in this sample. One patient (0.5%; 95% CI, 0–3) died within 72 hours of receiving a propofol infusion and was not related to the drug administration. This patient was 5 years old with diagnosis of posterior fossa tumor with preexisting bilateral strokes prior to PICU admission. The propofol infusion was stopped 7 hours before the patient's death along with the withdrawal of all life-sustaining therapy.

Twenty-nine patients (13%; 95% CI, 9–19) had at least one sign that mimics PRIS prior to the propofol infusion and were excluded from the adverse events/PRIS analysis. They all had metabolic acidosis at admission to the PICU or prior to receiving the propofol infusion. However, in all of these children, the acidosis resolved either before the infusion was started or while it was running. The dose and duration of propofol infusion in these children was similar to those who did not have signs that mimic PRIS prior to the infusion (data not shown). None of these patients developed PRIS.

DISCUSSION

The use of propofol in the PICU remains controversial. Since the first report of PRIS in 1990, numerous case reports/series and reviews of PRIS in critically ill patients have been published. A 2006 review of the U.S. Food and Drug Administration Adverse Event Reporting System from 1989 to April 2005 found that 21 patients younger than or 16 years old and 68 patients older than 16 years died after administration of propofol for nonprocedural sedation (13). This study concluded that at least 70% of the pediatric deaths and 30% of the adult deaths were similar to reports of PRIS in the medical literature. In 1999, in an unpublished, randomized controlled clinical trial, comparing propofol to standard sedative agents in PICU patients, a trend toward increased mortality in the propofol group was found despite similar baseline Pediatric Risk of Mortality scores between the groups (14–16).

However, further examination of previously published literature shows possible limitations to the evidence supporting the contraindication of propofol for sedation in pediatric critical care. The true prevalence of PRIS is unknown due to the varying definitions and presentations of PRIS and the lack of consistent reporting of all cases (15, 17). In a 2012 German survey of PICUs which reported seven cases of PRIS, definitions were not standardized (18). In the one case that additional information was available, the patient did not become bradycardic and therefore did not fulfill the criteria by Bray (6). Examination of previous reports of death from PRIS exhibits no pattern to the cause (16).

The effect of dose and duration of propofol in the development of PRIS has also been widely researched. Two retrospective studies using propofol as a bridge to extubation found that propofol was safe and effective at limiting doses to less than 4 mg/kg/hr (12, 19–21). In PICU patients in the retrospective study by Bray (6), PRIS developed in three of nine patients (33%), with the nine patients receiving an average infusion rate of 7.27 mg/kg/hr and for an average duration of 123.3 hours (6, 14). A retrospective review of adult ICU patients on propofol found that the prevalence of PRIS was dose dependent and did not occur in those receiving less than 5 mg/kg/hr but occurred in three of 18 patients (17%) receiving 5–6 mg/kg/hr and in four of 13 patients (31%) receiving more than 6 mg/kg/hr (22). In a prospective study in adult ICU patients, Roberts et al (23) found that PRIS developed in 11 of 1,017 patients (1.1%), with 18% of cases receiving more than 4.98 mg/kg/hr and a median infusion duration of 5 days. Although these studies used different criteria for their definitions, they all found that PRIS occurred in patients that received propofol at higher doses and for longer durations.

It is because of these differences that propofol use continues in PICUs for sedation despite contraindications. A survey of 45 physicians from 12 PICUs in Australia and New Zealand showed that 82% of responders used propofol in the PICU, 67% used infusion rates more than or equal to 10 mg/kg/hr, and 19% used propofol infusions for longer than 72 hours (24). A recent national survey of PICUs in Germany found that 79% of ICUs used propofol in children younger than 16 years old and more than 40% used it as a continuous infusion. Dose limits varying between 1 and 10 mg/kg/hr occurred in 51% of responding ICUs, with a median of 4 mg/kg/hr. Propofol was used for greater than 3 hours in 98% of units and 7% used it longer than 48 hours (18).

In our study, no patient on a propofol infusion developed PRIS. In our cohort, the use of propofol was not associated with hemodynamic instability, significant bradycardia, or lactic acidosis. This may be in part due to our local practice of using lower doses and shorter durations, which is consistent with previously published data. However, it is important to consider bolus dosing when calculating the total dose of propofol administered as median average hourly propofol dose increased 12% from 2.4 to 2.7 mg/kg/hr with bolus inclusion.

This study differs from previous retrospective reviews in a number of ways. As far as we are aware, this is the largest review of propofol use in PICU patients. As well, previous studies looking at the use of propofol as a bridge to extubation were specifically in pediatric burn patients (25) and those with congenital heart disease, both studies included only 11 children (20). Our study included a variety of PICU patients admitted for cardiac and respiratory reasons, representing a more general PICU population. As well, our study examined the compliance of actual propofol use with stated local practices.

The results should be interpreted with caution given study limitations. First, being a retrospective descriptive

cohort study with a relatively small sample (n = 223), we cannot rule out that other confounders could have affected the results. Concurrent use of other medications that may increase the risk of development or mask the signs and symptoms of PRIS was not collected in our study. In our PICU, patients that are started on a propofol infusion have any lipid infusions stopped and receive a dextrose-saline infusion. Some studies have suggested that inadequate carbohydrate intake during the infusion may increase the risk of developing PRIS; however, these practices were not captured as part of the study's data collection (26). This study reflects single-center practice in the use of propofol infusions, and it might not be applicable in other centers. Blood work in this study was only performed as ordered by the attending physician. Although data on bradycardia/asystole and metabolic acidosis was available for all patients, information on hepatomegaly, lipemic plasma, rhabdomyolysis, and myoglobinuria was not consistently recorded and thus could have occurred without being noted. Some authors have reported Brugada-like electrocardiogram changes with propofol administration which was not directly assessed in our study (27). The timeframe of data collection was based on previous data (12, 23) showing the median time to clinical manifestations of PRIS was 3 days. However, adverse events and the presence of PRIS could have been missed if they occurred later outside of the timeframe. In addition, different results may have been seen with the use of different definitions of PRIS reported. However, many definitions of PRIS are similar to the definition by Bray (6) , which requires the development of cardiac adverse effects. Since none of our patients developed bradycardia or asystole, it is unlikely that we would have found PRIS in our sample irrespective of the definition of PRIS used. We only examined each patient's first propofol infusion per admission; subsequent infusions were not included, so it is not known if that practice is associated with adverse events.

CONCLUSIONS

In this retrospective review of 223 propofol infusions initiated at admission at the Stollery Children's Hospital PICU, no cases of PRIS were noted when used at low doses and for short durations. The majority of the propofol infusions used were concordant with the local practice. The contribution of bolus doses to the hourly dose is important. Although this finding is positive in suggesting that restricted propofol use may be safe for sedation in critically ill pediatric patients, further large prospective randomized controlled trials are needed to definitively determine if higher doses, longer durations, and repeated propofol infusions cause increased prevalence of PRIS and death. As such, appropriate and consistent monitoring of adverse effects of propofol in critically ill pediatric patients is still warranted.

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