Sedation in pediatrics
Chapter 2

Propofol 6% as sedative in children under 2 years of age following major craniofacial surgery

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Br J Anaesth 2005;94:630-5
Abstract

Background: After alarming reports concerning deaths after sedation with propofol, infusion of this drug was contraindicated by the US Food and Drug Administration in children <18 yr receiving intensive care. We describe our experiences with propofol 6%, a new formula, during postoperative sedation in nonventilated children following craniofacial surgery.

Methods: In a prospective cohort study, children admitted to the pediatric surgical intensive care unit following major craniofacial surgery were randomly allocated to sedation with propofol 6% or midazolam, if judged necessary on the basis of a COMFORT-Behavior score. Exclusion criteria were respiratory infection, allergy for proteins, propofol or midazolam, hypertriglyceridemia, familial hypercholesterolemia or epilepsy. We assessed the safety of propofol 6% with triglycerides (TG) and creatine phosphokinase (CPK) levels, blood gases and physiological parameters. Efficacy was assessed using the COMFORT-Behavior scale, Visual Analogue Scale and Bispectral index™ monitor.

Results: Twenty-two children were treated with propofol 6%, 23 were treated with midazolam and 10 other children did not need sedation. The median age was 10 (IQR 3-17) months in all groups. Median duration of infusion was 11 (range 6-18) h for propofol 6% and 14 (range 5-17) h for midazolam. TG levels remained normal and no metabolic acidosis or adverse events were observed during propofol or midazolam infusion. Four patients had increased CPK levels.

Conclusion: We did not encounter any problems using propofol 6% as a sedative in children with a median age of 10 (IQR 3-17) months, with dosages < 4 mg kg⁻¹ h⁻¹, during a median period of 11 (range 6-18) h.

Introduction

Propofol for sedation in children has become controversial after reports describing the propofol infusion syndrome, which is characterized by increased triglyceride (TG) levels, myocardial failure, rhabdomyolysis, metabolic acidosis, hyperthermia and death. Therefore a warning was issued against use of propofol as a sedative in children < 18 years in intensive care. In Diprivan®-10, propofol is formulated in Intralipid® 10%. Long-term infusions of Diprivan®-10 have been associated with increases in serum lipid levels, notably TG. In order to reduce the volume and amount of lipids, a new formulation of propofol 6% in Lipofundin® MCT/LCT 10% (propofol 6%) was developed and tested in animals, adults and six children.

In contrast with propofol, midazolam is a widely used sedative for children. On initial administration, it has a short duration of action. However, paradoxical reactions such as agitation, convulsions, hyperactivity or adverse reactions have been reported in neonates and children. Also, the active metabolites and prolonged effect of midazolam often delay awakening and weaning from mechanical ventilation. A new formula for propofol would be an alternative or additional sedative in children receiving intensive care. In view of the existing controver-
sies, we present our experiences with propofol 6% as a postoperative sedative in nonventilated children < 2 yr of age following major craniofacial surgery.

Materials and Methods

With approval from the Erasmus MC research ethics board and written consent from a parent or legal guardian, from July 2002 until September 2003 we studied children aged between 1 month and 2 yr of age admitted to our pediatric surgical intensive care unit (PSICU) during the first 24 h after elective craniofacial surgery. Exclusion criteria for propofol were known allergies for proteins, egg or propofol, respiratory infections, hypertriglyceridemia, epilepsy, familial hypercholesterolemia or weight < 6 kg.

At least 1 day before surgery, the parents of eligible patients were asked to give written informed consent for either propofol or midazolam. If consent for propofol was refused, consent was asked for midazolam, even though midazolam is our standard of care. Four patients were excluded from receiving propofol on the ground of familial hypercholesterolemia, one patient was excluded as his TG level was 2.62 mmol litre\(^{-1}\) the day before surgery, probably because he had been fed just before blood sampling, and parents of two patients refused consent for propofol. These seven patients received midazolam for sedation instead of propofol.

Perioperative procedure

Anesthesia was induced with either sevoflurane or i.v. thiopental. An arterial line and a central venous line were placed for clinical purposes and blood was drawn to evaluate liver and kidney function, TG level and creatine phosphokinase (CPK) level. After i.v. administration of vecuronium 0.1 mg kg\(^{-1}\) and fentanyl 2.5 μg kg\(^{-1}\), the trachea was intubated and ventilated with air, oxygen and isoflurane. Approximately 2 h before anticipated extubation, acetaminophen 40 mg kg\(^{-1}\) was administered rectally as previously described.\(^{16}\) After surgery, the trachea was extubated and the patient was transferred to the PSICU, where heart rate, arterial pressure, oxygen saturation and central venous pressure were monitored continuously. Body temperature was measured every 2 h. Routine postoperative care included evaluation of haemoglobin, haematocrit, thrombocytes, white blood count and arterial blood gases. The children received no parenteral nutrition during the study period.

Sedation and analgesia protocol

On admission to the PSICU, usually in the early afternoon, sedation and analgesia levels were assessed using the COMFORT-Behavior scale and the Visual Analogue Scale (VAS). At COMFORT-Behavior scores < 17, no sedatives were given. At scores ≥ 17, propofol or midazolam was started. At VAS scores ≥ 4, more analgesia was given. During the first 2 h after start of sedation, sedation and analgesia levels were assessed at least three times using the COMFORT, VAS and Bispectral Index (BIS) values. After the first 2 h, the level of sedation was assessed every 2 h until the next morning. If the COMFORT-Behavior score remained ≥
17 after administration of a sedative, propofol and midazolam dosing were increased by 0.1 ml h\(^{-1}\) and 0.025 mg kg\(^{-1}\)h\(^{-1}\), respectively. If scores remained $\geq 17$ during propofol infusion of a maximum of 4 mg kg\(^{-1}\)h\(^{-1}\), midazolam was added. At scores $< 9$, propofol and midazolam dosing were decreased by 0.1 ml h\(^{-1}\) and 0.025 mg kg\(^{-1}\)h\(^{-1}\), respectively. At 8 a.m. the next morning, the sedatives were stopped to allow the patients to wake up and prepare for transfer to medium care. The effects of stopping the infusion were assessed using the COMFORT, VAS and BIS for the next 2 h. At approximately 11 a.m., all children were transferred to medium care.

**The COMFORT-Behavior scale**

The COMFORT-Behavior scale is an adapted version of the scale that was originally developed by Ambuel et al.\(^{17}\) in 1992 and consists of six behavioural items and two physiological parameters, heart rate and blood pressure. Marx et al.\(^{18}\) showed that this scale was useful to assess sedation. We showed that, leaving out the physiological items, the scale was still valid for both postoperative pain and sedation in children aged 0-3 yr.\(^{19}\) The COMFORT-Behavior scale assesses six patterns of behaviour: alertness, calmness, muscle tone, body movement, facial tension, crying (nonventilated children) or respiratory response (ventilated children). The total score ranges from 6 to 30: the higher the score, the more uncomfortable the child is. All nurses were trained to use the COMFORT-Behavior scale, as reported in our earlier analgesia study. Inter-observer reliability, represented by linearly weighted $\kappa$ was satisfactory, with $\kappa > 0.65$ for all nurses and principal investigator. A COMFORT-Behavior score $< 9$ represents oversedation, score between 9 and 17 represents no distress and $\geq 17$ represents distress.

**Bispectral index monitor**

Sedation was assessed continuously using a Bispectral A 2000 version 3.12 monitor (Aspect Medical Systems, Natick, MA, USA) with commercially available pediatric BIS sensors applied according to the manufacturer’s instruction manual. We used the impedance limits set in the monitor: if the signal quality index was $> 50$, the BIS value was recorded.

**Visual Analogue Scale**

To determine whether restlessness might be induced by pain, analgesia levels were assessed using the VAS. At VAS scores $\geq 4$, more analgesia was given. If the VAS score was $< 4$ and the COMFORT-Behavior $\geq 17$, a sedative was given.

**Determining safety**

Before, during and 2 h after stopping the infusion of propofol or midazolam, we determined TG and CPK levels to evaluate the influence of propofol on these variables. We used an enzymatic and colorimetric in vitro test, with a Hitachi analyser (Roche Diagnostics, GmbH, Mannheim, Germany). TG levels in the range 0-1.6 mmol litre\(^{-1}\) and CPK levels $< 230$ U litre\(^{-1}\) were considered normal.\(^{20}\) We defined desaturation as saturation $< 95\%$ for $> 5$ s and requiring intervention. Hypotension was defined as any period of time when a patient’s arterial pressure was 10-15% below the arterial pressure mentioned in Table 1. Bradycardia was defined as any
period of time when a patient’s heart rate was <80 beats min⁻¹ (see Table 1). Hyperthermia was defined as body temperature > 38.3°C. Metabolic acidosis was defined as arterial pH < 7.30 with a concomitant PaCO₂ < 4.7 kPa. All physiological parameters, except temperature, were screened hourly using a computer-guided patient data management system.

**Determining efficacy**
To compare efficacy of propofol with that of midazolam, we considered COMFORT-Behavior, VAS scores and BIS values in four groups: children receiving propofol, children receiving propofol with additional midazolam, children receiving midazolam and children who did not need sedation. Additionally, we determined the dose change frequency, i.e. the number of times that dosing of propofol or midazolam was adjusted.

**Medication preparation**
Propofol 6% was prepared in the Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands. Propofol 6% was given through the central venous line in order to prevent pain from injection. Midazolam hydrochloride was dissolved in glucose 5% to make an i.v. solution.

**Statistical analysis**
The data were analysed using SPSS for Windows (version 10.0; SPSS, Chicago, IL). The safety parameters of children receiving propofol 6% and those receiving no propofol 6% were compared using the Mann-Whitney U-test. Statistical differences were considered significant if \( P < 0.05 \). A correlation \( r \) of 0.10-0.29 was considered small, 0.30-0.49 was considered medium and \( \geq 0.50 \) was considered large.

**Table 1** Patient characteristics. Data are median (range). *N/a, not applicable

<table>
<thead>
<tr>
<th>Total</th>
<th>Propofol</th>
<th>Propofol + midazolam</th>
<th>Midazolam</th>
<th>No sedatives needed</th>
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</thead>
<tbody>
<tr>
<td>n=55</td>
<td>n=17</td>
<td>n=5</td>
<td>n=23</td>
<td>n=10</td>
</tr>
<tr>
<td>Patients, M/F</td>
<td>11 / 6</td>
<td>4 / 1</td>
<td>17 / 6</td>
<td>5 / 5</td>
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<tr>
<td>Age, months</td>
<td>9 (4-17)</td>
<td>12 (11-17)</td>
<td>11 (3-15)</td>
<td>9 (4-13)</td>
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<tr>
<td>Weight, kg</td>
<td>9 (6-13)</td>
<td>10 (9-10)</td>
<td>10 (5-12)</td>
<td>8 (6-10)</td>
</tr>
<tr>
<td>Duration of surgery, h</td>
<td>5 (4-7)</td>
<td>4 (4-5)</td>
<td>5 (3-7)</td>
<td>5 (3-6)</td>
</tr>
<tr>
<td>Duration of infusion of sedatives, h</td>
<td>12 (6-17)</td>
<td>10 (7-18)</td>
<td>13 (4-17)</td>
<td>*N/a</td>
</tr>
<tr>
<td>Doses, mg kg⁻¹ h⁻¹</td>
<td>2.4 (1.8-4.0)</td>
<td>Propofol 3.0 (1.8-3.6)</td>
<td>Midazolam 0.1 (0.05-0.10)</td>
<td>0.05 (0.05-0.20)</td>
</tr>
<tr>
<td>Baseline arterial pressure, mm Hg</td>
<td>55 (35-100)</td>
<td>50 (40-60)</td>
<td>51 (35-82)</td>
<td>52 (45-55)</td>
</tr>
<tr>
<td>Baseline heart rate, beats min⁻¹</td>
<td>129 (90-180)</td>
<td>127 (95-150)</td>
<td>113 (80-153)</td>
<td>121 (105-140)</td>
</tr>
</tbody>
</table>
**Results**

We studied 55 patients, with a median age of 10 (IQR 3-17) months and weight 9 (5-13) kg. Pre-operative diagnoses were scaphocephaly ($n=26$), trigonocephaly ($n=18$), brachycephaly ($n=2$), encephalocele ($n=1$), plagiocephaly ($n=5$) and Saethre-Chotzen syndrome ($n=3$). There was no significant differences between the groups with regard to age, weight, duration of surgery or duration of infusion of sedatives (Table 1).

In one patient the TG level was 2.00 mmol litre$^{-1}$ during propofol infusion without metabolic acidosis, disturbance in physiological parameters or increase of CPK levels (Figure 1). Four patients had raised CPK levels, ranging from 261 to 313 U litre$^{-1}$ during and after the end of infusion (Figure 2). Three patients had received propofol and one patient had no medication. Two patients receiving propofol had elevated CPK levels before the start of infusion and one of these patients had elevated CPK levels during and after infusion. The first patient had CPK levels of 261 U litre$^{-1}$ before infusion. The second patient had CPK levels of 336 U litre$^{-1}$ before infusion, 276 U litre$^{-1}$ during infusion and 240-282 U litre$^{-1}$ after infusion. One patient receiving propofol had a CPK level of 313 U litre$^{-1}$ after infusion. These patients showed no acidosis, no abnormal physiological parameters and no increased TG levels.

There were no respiratory complications. Three patients, one receiving propofol and two receiving midazolam, experienced short periods of desaturation with spontaneous recovery.

Median minimal arterial pressure was 56 mm Hg and 59 mm Hg for propofol 6% and no propofol 6%, respectively (Mann-Whitney $U$-test, 330; $P=0.57$). Median minimal heart rate was 110 beats min$^{-1}$ and 111 beats min$^{-1}$ for propofol 6% and no propofol 6%, respectively (Mann-Whitney $U$-test, 353; $P=0.86$). One episode of bradycardia lasting 90 s (median of 77 beats min$^{-1}$) was observed in a patient receiving midazolam. The median maximal temperature was 37.8ºC during propofol and 37.7ºC with no propofol (Mann-Whitney $U$-test, 352; $P=0.84$).

![Figure 1 Triglyceride levels](image-url)
A total of 915 paired COMFORT-Behavior scores, VAS and BIS values were obtained with a median of 15 (IQR 13-18) observations per patient. During infusion of propofol 6% median COMFORT and BIS values were 11 (9-18) and 78 (65-91), respectively. During infusion of midazolam, median COMFORT and BIS values were 11 (9-15) and 77 (63-91), respectively. VAS was ≥ 4 in only seven observations in seven children (less than 1% of all observations). The starting dose of propofol was sufficient in three children (< 14 %). A propofol infusion of 4 mg kg⁻¹ h⁻¹ was not sufficient in five cases (~ 23% of the propofol group), and these patients received additional sedation with either a single dose of midazolam (two patients), multiple doses (two patients) or continuous midazolam infusion (one patient) (median rate 0.05 mg kg⁻¹ h⁻¹).

One of the patients receiving midazolam became agitated and more restless after administration of up to 0.2-mg kg⁻¹ h⁻¹ maintenance infusion and five doses of midazolam.

**Discussion**

We did not encounter any problems with propofol 6% in dosages < 4 mg kg⁻¹ h⁻¹ in children with a median age of 10 (IQR 3-17) months during a median period of 11 (range 6-18) h. Propofol doses of 2 mg kg⁻¹ h⁻¹ were insufficient to maintain an adequate sedation level in > 86% of the children. Midazolam was insufficient in only 21% of the children. The TG level was 2.0 mmol litre⁻¹ in only one patient, during propofol infusion, without abnormalities in other physiological parameters. This patient had been fed with formula milk Nutrilon 1 (Nutricia, Zoetermeer, The Netherlands), just before blood sampling. Four other patients had increased
CPK levels, without other signs of the propofol infusion syndrome. An increase of the CPK level can also be a valid indication of the extent of muscle damage. Muscle damage due to major muscle-cutting surgery, such as craniofacial surgery, has been reported and should be taken into account when interpreting CPK levels postoperatively. CPK levels 10 times higher than normal are regarded as a warning sign for rhabdomyolysis.

A review of the literature yields reports both for and against the use of propofol as a sedative in children. Seventeen publications support propofol use in children at the pediatric intensive care unit (PICU). Pepperman and Macrae found no differences in mortality between propofol and other sedative agents in 198 children. Cornfield et al. described continuous infusion of propofol in 142 critically ill children, with a mean age of 5 yr 9 months. Ten showed metabolic acidosis and 10 died during the first week of propofol infusion. These deaths could all be attributed to the primary diagnosis. Martin et al. described nine children on mechanical ventilation receiving propofol for sedation and concluded that it was useful and safe. Knibbe et al. evaluated propofol for sedation for < 6 h sedation in six children aged 1-5 yr, following cardiac surgery, and found no adverse events. A number of authors have published guides to drug selection and use in the PICU. They acknowledge that propofol infusion may cause problems and therefore suggest avoiding it in patients with sepsis, respiratory infections or underlying metabolic problems, avoiding infusion for > 24 h and taking into account the lipid content of propofol when calculating patients’ daily caloric intakes.

Fourteen publications and one unpublished trial outline adverse events and deaths associated with propofol. Twelve publications pertain to children, four of which are case reports describing a total of eight children, aged from 4 weeks to 13 yr. Parke et al. reported five critically ill children who received propofol for > 90 h at a rate of > 5 mg kg h⁻¹ and died. The high doses and long duration may explain these deaths. Regrettably, these case reports reveal no details on use of parenteral feeding. Bray reviewed propofol infusion in a PICU and found a significant association between long-term high-dose propofol infusion and the development of progressive myocardial failure. However, full details on comorbidity and parenteral feeding are lacking. Bray, Cray et al. and Cravero (unpublished data) expressed concerns about propofol as a sedative in children. Strickland et al. reported an 11-year-old girl with an astrocytoma who died after long-term propofol infusion. However, a cause-and-effect relationship could not be determined. More recently, Koch et al. described a 5-year-old child receiving short-term propofol infusion at a high rate who developed lactic acidosis.

Based on 14 publications, describing 27 patients, and one unpublished trial, the US Food and Drugs Administration contraindicated propofol for sedation of children < 18 yr receiving intensive care. However, 17 other publications appeared in support of propofol, reviewing a total of 395 patients without evidence for a relationship between propofol infusion and death. This paper describes a prospective cohort study comparing safety and efficacy of propofol and midazolam in children < 2 yr. Clearly, our study has limitations. First, the number of children receiving propofol 6% in this study is too small to allow conclusions to be drawn. Reviewing the total of 422 children, described in the above publications with regards to safety, eight children (< 2%) had evidence of propofol infusion syndrome. Thus, to encounter one child with the propofol infusion syndrome, we would have had to include at least 50 patients...
receiving propofol. Secondly, all studied children were healthy, apart from their major cranio-facial deformities. Therefore these children are not representative of the general ICU population. Thirdly, the children received low doses of propofol; higher doses might have produced adverse events. Fourthly, blinding was not possible in this study, because of propofol’s characteristic consistency. Fifthly, randomization was aimed at but failed due to unforeseen logistic reasons.

Despite the limitations of our study, it is important to note that we did not encounter any problems using propofol 6% as a sedative with dosages less than 4 mg kg\(^{-1}\) h\(^{-1}\) in children with a median age of 10 (IQR 3-17) months during a median period of 11 (6 to 18) h in postoperative patients without multiple organ failure or critical illness. Based on this study, it is too early to state that propofol is safe for sedation in children. However, we believe that it is important to share our experiences with propofol 6% and call for randomized controlled trials in pediatric patients to establish the safety of propofol as a sedative.

References
