

## Propofol: Effective Dose and Induction Characteristics in Unpremedicated Children

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The induction dose, induction characteristics, and cardiovascular and respiratory effects of propofol were studied in 90 unpremedicated children 3–12 yr old. Propofol in a dose of 1–3 mg · kg<sup>-1</sup> was injected in an antecubital vein over 10–30 s. Successful induction was defined by loss of eyelash reflex occurring within 50 s of the conclusion of propofol injection and followed by subsequent acceptance of face mask without excessive movement. The effective dose of propofol resulting in loss of eyelash reflex in 50% (ED<sub>50</sub>) and 95% (ED<sub>95</sub>) of children were 1.3 (1.1–1.4) and 2.0 (1.7–2.6) mg · kg<sup>-1</sup> (95% confidence interval). The corresponding ED<sub>50</sub> and ED<sub>95</sub> for a successful induction that included acceptance of face mask were 1.5 (1.3–1.7) and 2.3 (2.1–3.0), respectively. There was a 6.6% incidence of mild to moderate pain on injection and a 12.7% incidence of involuntary movement. Apnea (cessation of breathing >20 s) was seen in 21% of patients. Blood pressure decreased by more than 20% of baseline value in 48% of patients who received halothane (1–3%) after the bolus injection of propofol. It is concluded that propofol is an effective induction agent in children. A dose of 2.5–3.0 mg · kg<sup>-1</sup> is recommended to ensure a smooth transition to an inhalational maintenance technique. The use of antecubital veins is associated with a low incidence of pain on injection. (Key words: Anesthetics, intravenous: propofol. Anesthetic techniques: induction. Anesthesia, pediatric.)

PROPOFOL is a new intravenous (iv) anesthetic that has recently been released in this country. It has been shown to be effective for induction and maintenance of anesthesia in clinical trials with over 5,000 adult patients worldwide.

This study examined the efficacy of various induction doses, the induction characteristics, and the cardiovascular and respiratory effects of propofol when used in a single-induction dose, followed by N<sub>2</sub>O and halothane inhalation, in three age groups of unpremedicated children.

### Materials and Methods

Institutional approval and parental consent were obtained for this open, noncomparative randomized study

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to determine the effective induction dose of propofol. The protocol required 90 patients, with the provision that nonevaluable subjects be replaced. To meet this requirement, a total of 91 children received the drug. All of the study patients were healthy ASA physical status 1 or 2 children scheduled to undergo elective surgical procedures not expected to exceed 1 h in duration. No preoperative medication was used.

To encourage the acceptance of an iv induction technique and participation in the study, a 24-G catheter was inserted by an anesthesiologist in an antecubital vein and used for preoperative phlebotomy (for complete blood count) instead of sending the child to the laboratory. The catheter was then flushed with dilute heparin solution and later used to inject the induction dose of propofol without the need for a separate venipuncture.

Patients selected for the study were stratified into three age groups: 3–5, 6–8, and 9–12 yr. Within each age group, the children were randomly assigned to receive one of five possible induction doses of propofol: 1, 1.5, 2, 2.5, or 3 mg · kg<sup>-1</sup> injected over 10–30 s. Six patients, therefore, were entered into each dose group for a total of 30 patients per age group. The presence of eyelash reflex was tested every 10 s after drug injection. Onset of sleep was defined by loss of eyelash reflex within 50 s of the conclusion of propofol administration. Subsequent response to gentle application of a face mask delivering 60% N<sub>2</sub>O and 1% halothane was judged to be excellent if it resulted in no movement, acceptable if it resulted in some movement but did not require removal of the mask, or unacceptable if the child moved excessively or pushed the mask away. Testing of eyelash reflex and mask acceptance was performed by a second anesthesiologist, who was not involved in the administration of propofol.

A successful induction was defined by loss of eyelash reflex within 50 s, followed by excellent or acceptable response to the face mask. Patients in whom induction was judged not successful after the initial dose received up to two additional boluses, each equal to 50% of the original dose, as needed. Only the original, randomly assigned dose of propofol was used for statistical comparison. If present, pain or discomfort at the site of injection during or after propofol administration were recorded and graded by the anesthesiologist who had injected the drug as mild, moderate, or severe according to the patient's facial expressions, arm movements, or complaints of pain. The respiratory rate was monitored by impedance pneu-

mography. If apnea occurred, controlled ventilation of the lungs was instituted 20 s after the onset of the apnea episode.

Anesthesia was maintained with halothane (1–3%) and N<sub>2</sub>O (60% in oxygen). Succinylcholine (2.0 mg · kg<sup>-1</sup>) iv or atracurium (0.5 mg · kg<sup>-1</sup>) iv was administered for patients who required tracheal intubation. All subsequent iv medications and solutions were injected through a separate iv catheter that was inserted in a separate site after the child was asleep. This was done to evaluate the venous sequelae of propofol injection without the possible confounding effect of other potentially irritating medications, e.g., antibiotics that needed to be injected during or after surgery.

Baseline values obtained in the preoperative holding area and subsequent changes in heart rate, blood pressure, respiratory rate, and hemoglobin oxygen saturation (SpO<sub>2</sub>) were recorded by an independent observer every 1 min for the first 10 min after propofol injection and every 10 min thereafter until the end of surgery. The injection site was examined 24 h later for possible phlebitis, irritation, or thrombosis. Findings were described and recorded.

Demographic variables were compared among age groups by using Kruskal-Wallis tests for continuous variables and chi-squared or Fisher's exact tests for discrete variables. The data on eyelash reflex response and face mask tolerance were evaluated first by logistic multiple regression analysis to test the effect of age. The response data then were analyzed by logit analysis for all patients. The effective dose of propofol (in milligrams per kilogram) that resulted in loss of eyelash reflex as well as the dose that resulted in a successful induction (including mask acceptance) in 50% (ED<sub>50</sub>) and 95% (ED<sub>95</sub>) of patients were estimated and their 95% confidence intervals obtained from the logit analysis. The association between dose and the occurrence of apnea was examined by Mantel-Haensel's chi-square test.  $P < .05$  was considered significant.

## Results

No age related differences were observed and therefore results are presented for the entire group. The ED<sub>50</sub> and

TABLE 1. ED<sub>50</sub> and ED<sub>95</sub> of Propofol

Response	ED <sub>50</sub> (mg · kg <sup>-1</sup> )	ED <sub>95</sub> (mg · kg <sup>-1</sup> )
Loss of eyelash reflex (sleep)	1.3 (1.1–1.4)	2.0 (1.7–2.6)
Successful induction (sleep and mask acceptance)	1.5 (1.3–1.7)	2.3 (2.1–3.0)

Confidence intervals are 95%.

TABLE 2. Correlation between Propofol Induction Dose and Apnea of ≥20 s

Induction Dose (mg · kg <sup>-1</sup> )	Number of Patients Developing Apnea	%
1.0	0	0
1.5	0	0
2.0	3	16
2.5	3	16
3.0	6	32
Total	12	21

Data are shown for patients to whom no muscle relaxants were administered.

ED<sub>95</sub> of propofol that resulted in loss of eyelash reflex as well as the ED<sub>50</sub> and ED<sub>95</sub> that resulted in a successful induction (including mask acceptance) are shown in table 1.

Involuntary or semipurposive movements were observed in 12.7% of patients who had successful induction. Six patients (6.6%) complained of mild to moderate pain during injection of propofol. There were no incidents of severe pain that resulted in withdrawal or that otherwise required further intervention.

No evidence of any venous sequelae at the injection site was seen.

Apnea occurred in 21% of the patients who did not receive a muscle relaxant immediately after loss of eyelash reflex (n = 57). The number of patients who had apnea is presented in table 2. Apnea occurred only in the groups receiving 2.0, 2.5, or 3.0 mg · kg<sup>-1</sup>. The correlation between the occurrence of apnea and dose was not significant ( $P = 0.08$ ).

Forty-eight percent of the patients had a 20% or greater decrease in blood pressure 1–10 min after propofol administration at the same time that halothane (1–3%) was introduced. Sixty-nine percent of the hypotensive episodes began 4 min or later after the end of the bolus injection. All episodes of hypotension resolved to within 20% of control blood pressure with reduction of the inspired halothane concentration. Heart rate was not significantly different ( $\pm 20\%$ ) from baseline values during the induction period. Three patients developed a bigeminal rhythm during anesthesia maintenance that was treated by decreasing the inspired halothane concentration and hyperventilation. One patient developed laryngospasm during induction that was treated with the administration of a muscle relaxant and controlled ventilation. Six children had one or more episodes of postoperative vomiting. There were no other observed adverse reactions or complaints from any patient.

## Discussion

Smooth induction of anesthesia in unpremedicated children is a challenge for anesthesiologists. Although in

this country the most frequent choice is an inhalation induction, iv induction is used occasionally, and in many cases is preferred by older children.<sup>1</sup>

When administered intravenously, propofol produces a dose-dependent depression of central nervous system function. Its ability to produce loss of consciousness depends both on the dose and on the rate of drug administration.<sup>2,3</sup> Studies in adults have shown that with an induction dose of 2–2.5 mg · kg<sup>-1</sup> iv, loss of consciousness occurs within one arm-to-brain circulation time (<60 s). Experience in children is still limited. Most of the available studies were performed on premedicated children<sup>3–6</sup> or involved the use of other medications (e.g., iv lidocaine or eutectic mixture of local anesthetics (EMLA) cream)<sup>4,7</sup> at the time of induction. The results of the current study indicate that propofol is an effective induction agent in young unpremedicated children.

In attempts to assess the satisfactory onset of anesthesia, loss of eyelash reflex is commonly used as an end point after the injection of iv induction agents.<sup>4</sup> However, this sign has been reported to be of varying reliability in adult studies with propofol.<sup>4,8</sup> As a practical matter, iv induction in children is followed by application of a face mask, and the success of the induction is judged usually according to the smoothness of that transition. A dose range of 2.5–3.0 mg · kg<sup>-1</sup> therefore is recommended to induce sleep and to ensure successful acceptance of mask application. This dose is considerably lower than the 3.5–4.0 mg · kg<sup>-1</sup> recommended by Patel *et al.* in a recent study that included both premedicated and nonpremedicated children.<sup>4</sup> The difference may be explained in part by our allowance of up to 50 s to assess the adequacy of an induction dose, compared to the 20 s allowed by Patel *et al.*<sup>4</sup>

The incidence of pain on injection, which has been reported to be as high as 44% when hand veins are used,<sup>3</sup> was seen infrequently (<7%) and when present was mild or moderate in intensity in patients who had propofol injected into the larger antecubital veins. Pain on injection during induction of anesthesia with propofol depends in great part on the site of administration.<sup>9</sup> It has been reported to be as high as 31% when the veins on the dorsum of the hand were used, as compared to 8% when the antecubital veins were used.<sup>7</sup> Other authors, however, still reported a 24% incidence of pain even when propofol was injected in an antecubital vein in premedicated children.<sup>5</sup> The severity of pain is not related to the speed of injection<sup>3</sup> and, if a small hand vein is chosen, can be greatly reduced if lidocaine either is mixed with propofol or is administered into the iv catheter prior to the injection of propofol.

The incidence of apnea with propofol in our patients was comparable to that reported by others.<sup>5</sup> It did not

prove to be a problem since it did not interfere with the continuation of induction with an inhalational agent.

Studies of the cardiovascular effects of propofol when it is used for induction of anesthesia in children have found the decrease in blood pressure to be similar to that observed after thiopental.<sup>7,10</sup> The subsequent administration of halothane may increase the incidence and/or the magnitude of hypotension, and it may have contributed to the 48% incidence of hypotension in our patients, since 68.8% of the children who became hypotensive did so 4 min or more after the end of the bolus injection. A lower incidence of hypotension has been reported when propofol injection was followed by N<sub>2</sub>O administration for 5 min before a potent inhalational agent was introduced.<sup>10</sup> The decrease in systolic blood pressure when propofol induction was followed by halothane inhalation was well tolerated by our group of otherwise healthy children and required no other intervention than reducing the inspired halothane concentration. The cardiovascular response in small infants or hypovolemic patients may be more profound.

In conclusion, propofol is an effective induction agent in young unpremedicated children. The use of large antecubital veins is associated with a low incidence of pain on injection. A dose range of 2.5–3.0 mg · kg<sup>-1</sup> is recommended to induce sleep and assure smooth transition to administration of inhaled anesthetics by face mask.

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