Propofol decreases cerebral blood flow velocity in anesthetized children

[Le propofol diminue la vitesse circulatoire cérébrale chez les enfants anesthésiés]

Cengiz Karsli BSc MD FRCPC, Igor Luginbuehl MD, Mark Farrar MB BS FRCA, Bruno Bissonnette BSc MD FRCPC

Purpose: Propofol, by virtue of its favourable pharmacokinetic profile, is suitable for maintenance of anesthesia by continuous infusion during neurosurgical procedures in adults. It is gaining popularity for use in pediatric patients. To determine the effects of propofol on cerebral blood flow in children, middle cerebral artery blood flow velocity (Vmca) was measured at different levels of propofol administration by transcranial Doppler (TCD) sonography.

Methods: Twelve ASA I or II children, aged one to six years undergoing elective urological surgery were randomized to receive one of two propofol dosing regimens. Half of the patients received propofol in an escalating fashion, initially targeting an estimated steady-state serum concentration of 3 $\mu g \cdot mL^{-1}$, which was then doubled. The other half received propofol designed initially to target the high concentration followed by the lower one. In each child anesthesia was induced and maintained with propofol according to the protocol, rocuronium was given to facilitate tracheal intubation, and a caudal epidural block was performed. A TCD probe was placed appropriately to measure Vmca. Cerebral blood flow velocity (CBFV), mean arterial pressure (MAP) and heart rate (HR) were recorded simultaneously at both levels of propofol administration.

Results: Twelve patients were studied. At the higher estimated target serum propofol concentration there were significant decreases in Vmca (17%, $P < 0.001$), MAP (6%, $P < 0.002$) and HR (8%, $P < 0.05$) when compared to the lower targeted concentration.

Conclusion: This study shows that a higher rate of propofol infusion is associated with lower CBFV and MAP values in children. Propofol's cerebral vasoconstrictive properties may be responsible for this finding.

Objectif : *En vertu de son profil pharmacocinétique favorable, le propofol convient bien au maintien de l'anesthésie administrée en perfusion continue pendant des interventions neurochirurgicales chez les adultes. On l'utilise également de plus en plus en pédiatrie. Dans le but de déterminer les effets du propofol sur la vitesse circulatoire cérébrale chez les enfants, nous avons mesuré par échographie Doppler transcrânienne (DTC) la vitesse circulatoire de l'artère cérébrale moyenne (Vacm) selon différents niveaux de propofol.*

Méthode : *Douze enfants, de un à six ans, d'état physique ASA I ou II devant subir une intervention urologique non urgente, ont été répartis au hasard et ont reçu l'un des deux schémas posologiques de propofol. La moitié des patients a reçu du propofol de manière croissante, en visant initialement une concentration sérique estimée, à l'état d'équilibre, à 3 $\mu g \cdot mL^{-1}$ et qui a été ensuite doublée. Les autres enfants ont reçu du propofol de manière à atteindre d'abord une forte concentration, suivie d'une plus faible. L'anesthésie a été induite et maintenue avec du propofol d'après le protocole et du rocuronium a été administré pour faciliter l'intubation endotrachéale. Enfin, on a procédé à une anesthésie caudale. Une sonde à DTC a été placée de manière à mesurer la Vacm. La vitesse circulatoire du sang cérébral (VCSC), la tension artérielle moyenne (TAM) et la fréquence cardiaque (FC) ont été enregistrées simultanément, pour les deux concentrations de propofol administrées.*

Résultats : *Des baisses significatives de Vacm (17 %, $P < 0,001$), de TAM (6 %, $P < 0,002$) et de FC (8 %, $P < 0,05$) ont été notées avec la plus forte concentration sérique de propofol visée, comparée à la plus faible.*

Conclusion : *L'étude montre qu'une perfusion de propofol à débit élevé est associée à des valeurs de VCSC et de TAM plus faibles chez les enfants. Les propriétés vasoconstrictrices cérébrales du propofol peuvent être responsables de ce résultat.*

PROPOFOL is used increasingly for the induction and maintenance of anesthesia in children. Its use is characterized by rapid clearance and distribution, resulting in rapid emergence from anesthesia,[1] and decreased nausea and vomiting.[2] Propofol is a suitable agent for neuroanesthesia in adult patients[3] and is gaining popular-

From the Department of Anesthesia, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.
Address correspondence to: Dr. B. Bissonnette, Department of Anesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. Phone: 416-813-7445; Fax: 416-813-7543; E-mail: bruno@anaes.sickkids.on.ca
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ity in the pediatric population.[4] The increase in popularity of *iv* techniques for neuroanesthesia in children results from potentially undesirable cerebral vasodilatory effects of the volatile anesthetic agents at higher concentrations.[5]

Studies in adults using ^{133}Xenon (Xe) inhalation scintillography have demonstrated that propofol causes a significant decrease in cerebral blood flow and increases cerebral vascular resistance.[6] Transcranial Doppler (TCD) studies have reported that cerebral blood flow velocity (CBFV) is decreased in adult patients receiving a propofol infusion, when compared to awake controls.[7] The effect of propofol on CBFV in children remains unclear. The aim of this study was to test the hypothesis that a higher rate of propofol administration is associated with lower CBFV values in children, as measured by TCD sonography.

Methods

With Regional Ethics Board approval and written parental consent, 12 unpremedicated children aged one to six years, ASA I or II, undergoing urological surgery under general anesthesia were enrolled. Patients with cardiovascular or neurological disease, a history of premature birth or contraindication to regional anesthesia were excluded. All patients were randomized into two groups using a computerized random table number. In each child, an *iv* catheter was inserted after administration of 70% nitrous oxide in oxygen, standard anesthetic monitors were applied, propofol was given according to the study protocol as described below, and tracheal intubation was facilitated with rocuronium 1.0 $mg \cdot kg^{-1}$. Intermittent positive pressure ventilation was instituted with 30% oxygen in air. Peak airway pressure, ventilatory rate and end-tidal CO_2 ($P_{ET}CO_2$) were kept constant throughout the study. All subjects received a caudal epidural block with 1.0 $mL \cdot kg^{-1}$ of 0.25% bupivacaine without adrenaline in order to block the cerebrovascular response to surgical stimulation during the study period. Surgery was then allowed to commence, and a TCD probe was placed appropriately to measure middle cerebral artery blood flow velocity (Vmca) at the M1 segment using a 2 MHz emitted ultrasonic frequency. In half of the patients anesthesia was induced with propofol 2.5 $mg \cdot kg^{-1}$, followed by an infusion of 15 $mg \cdot kg^{-1} \cdot hr^{-1}$ for the first 15 min, 13 $mg \cdot kg^{-1} \cdot hr^{-1}$ for the next 15 min, and 11 $mg \cdot kg^{-1} \cdot hr^{-1}$ from 30–60 min. This was based on a pediatric pharmacokinetic model designed to target an estimated steady-state serum propofol concentration of 3 $\mu g \cdot mL^{-1}$.[2] Thirty minutes were allowed for steady state to be reached, at which point three measurements of Vmca, heart rate (HR) and mean arterial pressure (MAP) were taken at one-minute intervals. In order to double the estimated serum propofol concentration, another 2.5 $mg \cdot kg^{-1}$ of propofol was given, and the infusion was doubled to 22 $mg \cdot kg^{-1} \cdot hr^{-1}$. Another 30 min were allowed to establish steady state, and Vmca, HR and MAP were again recorded three times at one-minute intervals.

In the other half of the patients anesthesia was induced with propofol 5 $mg \cdot kg^{-1}$, followed by an infusion of 30 $mg \cdot kg^{-1} \cdot hr^{-1}$ for the first 15 min, 26 $mg \cdot kg^{-1} \cdot hr^{-1}$ for the next 15 min, and 22 $mg \cdot kg^{-1} \cdot hr^{-1}$ from then on. Thirty minutes were allowed for steady state to be reached, at which point the same variables were recorded at one-minute intervals. In order to lower the estimated serum propofol concentration to 3 $\mu g \cdot mL^{-1}$, the infusion was stopped for five minutes, and restarted at 11 $mg \cdot kg^{-1} \cdot hr^{-1}$. Another 30 min were allowed for the new steady state to be reached, and Vmca, HR and MAP were again recorded three times at one-minute intervals. In all patients body temperature was monitored rectally and maintained constant with a conductive water mattress and convective air warmer under the surgical drapes. The subjects were supine and horizontal throughout the study period.

The number of patients needed to demonstrate a direct effect on CBFV during changes in propofol dosing was calculated with the assumption that a 20% change would be clinically relevant. Based on a statistical power of 0.8, an $\alpha_2 = 0.05$ and a ß = 0.2, a total of seven patients was suggested. Twelve patients were studied to account for methodological difficulties that could have led to exclusion from the study. Demographic and parametric data are expressed as mean ± SD. Within group analysis of Vmca, HR and MAP data was achieved using the student unpaired t test, and between groups analysis was performed using ANOVA and the student Newman Keuls test for multiple comparisons. Analysis of TCD measurements was carried out by an investigator unaware of the sequence of propofol administration. A $P < 0.05$ was accepted for statistical significance.

Results

Twelve patients were studied, with an average age and weight of 3.2 ± 1.9 yr and 15.7 ± 5.8 kg, respectively. The caudal block seemed to be successful in all cases and TCD measurements were completed in all children.

At the higher estimated target serum propofol concentration there were significant decreases in Vmca (17%, $P < 0.001$), MAP (6%, $P < 0.002$) and HR (8%, $P < 0.05$) when compared to the lower targeted concentration (3 $\mu g \cdot mL^{-1}$; Figure 1). Typical CBFV tracings for both the low and high propofol concentrations are shown in Figure 2. There were no complications that resulted from this study.

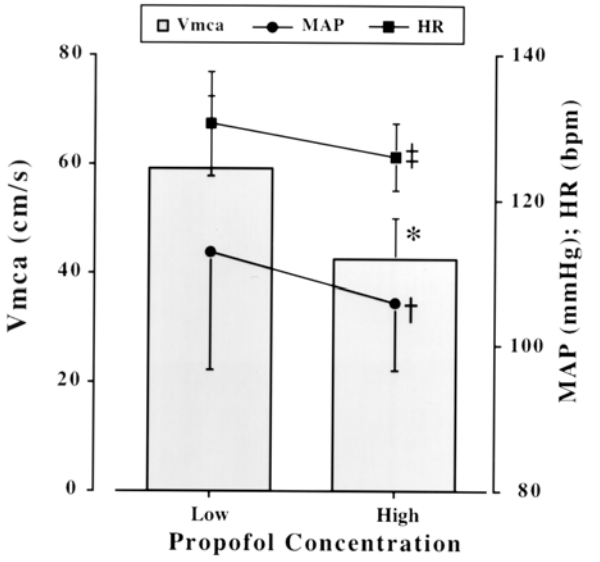

FIGURE 1 Changes in Vmca, MAP and HR at the low (3 μg·mL^{-1}) and high estimated steady state serum propofol concentrations. *P < 0.0001; †P <0.002; ‡P <0.05. Vmca = middle cerebral artery blood flow velocity = Vmca = middle cerebral artery blood flow velocity; MAP = mean arterial pressure; HR = heart rate.

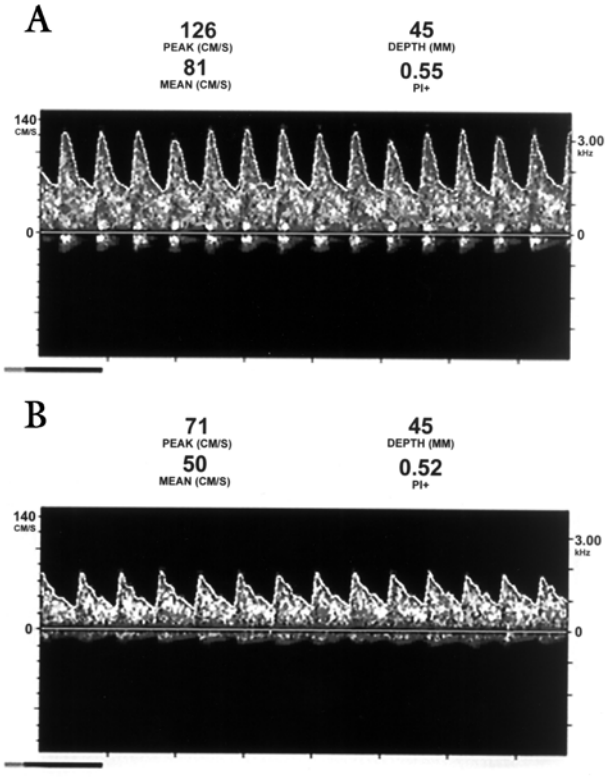

FIGURE 2 Typical Vmca tracings at low (A) and high (B) estimated steady-state serum propofol concentrations. Vmca = middle cerebral artery blood flow velocity; PI = pulsatility index; kHz = kilohertz.

Discussion

This study shows that in children, a higher rate of propofol infusion results in lower CBFV and MAP values without an accompanying compensatory increase in HR. Regardless of the actual serum propofol concentrations that were obtained, this study at least confirms that there is a relationship between propofol dosing and CBFV in children. Furthermore, the decrease in CBFV outweighed the drop in MAP. These findings seem to be in agreement with similar adult studies. TCD studies have shown that in adults propofol causes significant decreases in CBFV without decreasing MAP.[7] The authors of that study concluded that propofol has vasoconstrictive properties on the cerebral vasculature. Propofol has been shown to decrease cerebral blood flow and increase cerebral vascular resistance in healthy adults even when MAP was kept constant with the use of a phenylephrine infusion.[6] In the present study the fact that the decrease in CBFV outweighed the drop in MAP suggests that propofol may cause cerebral vasoconstriction in children as well. A recent pediatric cerebrovascular CO_2 reactivity study using propofol supports this hypothesis.[9] In addition, since McAuliffe *et al.* have shown that cardiac output is HR dependent in infants and children,[10] the noted decrease in MAP may have been partly due to a decrease in HR.

Propofol seems to demonstrate many of the properties of an ideal anesthetic agent for adults undergoing neurosurgical procedures, as it has been shown to decrease both cerebral metabolism and blood flow.[6] In addition, its rapid metabolic clearance provides for an early, predictable and complete recovery, making propofol suitable for maintenance of anesthesia by continuous infusion.[11] The propofol dosing regimen used in the present study was adapted from published pharmacokinetic studies of propofol infusion data in children.[12–15] For the "low" propofol concentration arm of the study, a manual infusion regimen capable of maintaining an estimated steady state blood concentration of 3 μg·mL^{-1} in children was used.[8] This same target concentration has been chosen in several adult studies.[16–18] The blood propofol concentration required to achieve sedation or anesthesia is very similar in both children and adults.[19] Due to significant pharmacokinetic and pharmacodynamic differences between children and adults however, propofol doses and infusion rates required to achieve a certain target blood concentration are higher for pediatric

patients.[13,16] In addition, the context-sensitive half-life of propofol is longer in children than in adults, presumably due to altered compartment volumes of distribution.[8] This implies that recovery from a propofol infusion will be slower in children than in adults, which may limit its usefulness in prolonged neurosurgical procedures. Further evaluation aimed at validating this propofol infusion regimen might be beneficial. Pediatric propofol pharmacokinetic studies carried out by Kataria *et al.*[15] and Short *et al.*[14] have shown that upon discontinuation of a 30-min infusion, serum propofol levels decrease by 50% in well under ten minutes. The propofol dosing adjustment strategy used in the present study was derived in part from findings reported in these pharmacokinetic studies.

Several physiological factors have been shown to alter CBFV, including $P_{ET}CO_2$, cardiac output, surgical stimulation, body temperature and intra-thoracic pressure.[20] End-tidal CO_2 and body temperature remained unchanged throughout the study period, and any cerebrovascular effects of surgical stimulation seemed to have been successfully eliminated by the caudal epidural block, although this cannot be excluded with certainty.

There are some methodological considerations that need to be addressed. Although TCD sonography is a simple non-invasive method of measuring CBFV, it is not a direct measure of cerebral blood flow. However, studies measuring ^{133}Xe clearance and radioactive microspheres have shown that relative changes in CBFV correlate well with changes in cerebral blood flow.[21,22] TCD sonography is now widely used as a surrogate measure of cerebral blood flow.[23] Interpatient variability in CBFV measurements can be due to variations in Doppler probe positioning, resulting in different angles of insonation (i.e., the angle at which the Doppler beam impacts on the artery). Intrapatient variability may result if the probe position changes during the course of a study. Thus in order to minimize these errors an experienced user fixed the Doppler probe to the subject's head using a custom designed frame.[6]

In conclusion, the present study shows that increasing the rate of propofol infusion in children results in a 17% decrease in CBFV that outweighs the reduction (6%) in MAP. Propofol's cerebral vasoconstrictive properties may be primarily responsible for this decrease in CBFV, however further evaluation will be necessary to confirm this hypothesis. Although propofol demonstrates, in theory, the properties of an ideal neuroanesthetic agent, additional dosing validation studies and direct clinical comparison to volatile agents are needed before this claim can be made for pediatric neurosurgical patients.

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