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Pharmacokinetics and pharmacodynamics of propofol in children undergoing different types of surgeries

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ABSTRACT

Background: Propofol is a commonly used agent in total intravenous anesthesia (TIVA). However, the link between its pharmacokinetics and pharmacodynamics has not been fully characterized in children yet. Our aim was to determine the quantitative relationship between the venous plasma concentration and bispectral index (BIS) effect in a heterogeneous group of pediatric patients undergoing various surgical procedures (ASA status I–III).

Methods: Nine male and nine female patients were anesthetized with propofol–fentanyl TIVA. Sparse venous samples for propofol concentrations assay and dense BIS measurements were collected during and after the end of infusion. Nonlinear mixed-effect modeling in NONMEM was used for data analysis.

Results: A three-compartment model was linked with a classical E_{max} model through a biophase compartment to describe the available data. All clearance and volume terms were allometrically scaled to account for the body mass difference among the patients under study. A typical patient had their PK parameters observed within the range of literature values for children. The pharmacodynamic parameters were highly variable. The EC_{50} of 2.80 mg/L and the biophase distribution rate constant of 3.33 min^{-1} were found for a typical patient.

Conclusions: The BIS values in children are highly correlated with the propofol effect compartment concentrations according to the classical E_{max} concentration–response relationship. Children had slightly lower sensitivity to propofol and slightly higher clearance, as compared with the adult data available in literature. The intra-patient variations in the BIS require the anesthesiologist's attention in using BIS values alone to evaluate the depth of anesthesia in children.

Introduction

In the past decade the role of total intravenous anesthesia (TIVA) in children increased as many advantages of this technique were reported. For example, postoperative nausea and vomiting are undeniably reduced in the presence of a TIVA anesthetic, as compared with any inhalational anesthetic. Organ toxicity is more likely to occur with inhalational anesthetics rather than intravenous medications [1]. As pharmacodynamic (PD) parameters in children are still debated, up to now there has been no pharmacokinetic/pharmacodynamic (PK/PD) model of propofol available for pediatric anesthesia [2,3]. A pharmacodynamic feedback, such as the bispectral index (BIS), may be useful to counteract interindividual variability in the pediatric population. The technology of BIS monitoring has long been questioned in children [4], however it has become more popular as more research has been done on the subject of relating propofol concentrations with BIS measurements [5–9]. Many factors

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influencing the BIS during propofol infusion have not been fully elucidated yet, especially those concerning the time to peak effect and the biophase distribution rate constant [10].

Also, the pharmacokinetics (PK) of propofol requires further studies. High variability in the PK and PD can be observed in children, especially in critical care settings. The PK parameters of propofol change dynamically with age and children of different ages cannot be treated in the same way. Within the first year of the child's life the body weight-scaled clearance approaches adult values [11]. For older children the weight is mostly used as a covariate to explain the observed inter-patient variability. Several models have already been proposed for children [12–17], with the one by Kataria et al. being the most commonly used. In the model by Kataria et al. the PK of propofol was studied on 53 healthy, unpremedicated children aged from 3 to 11 years. Two administration protocols were used – the first was an intravenous bolus of 3.5 mg/kg, and the other was the same bolus followed by the infusion at a rate ranging from 0.125 mg/kg/min to 0.20 mg/kg/min. A three-compartment model was used to characterize propofol disposition. In this study weight was found to be an important covariate for all PK parameters. Age improved the fit only moderately. The studies by Rigouzo et al. published in 2010 proved that the Schnider model, which is recommended to adults, may also be useful in pediatrics, in children aged between 6 and 12 years [10,14,18].

Propofol is predominantly metabolized in the liver, mainly by glucuronosyltransferase UGT1A9. The secondary metabolic cascade, mainly mediated by CYP2B6 and to a lesser extent by CYP2C9, leads to the production of 4-hydroxypropofol, which is further metabolized by conjugation. The existence of extra-hepatic metabolism is also taken into consideration. Takata et al. suggested that the organs responsible for its metabolism are the kidneys, small intestine, brain and lungs, where the kidneys were ascribed the most significant role. The high value of the hepatic extraction ratio suggests that the clearance of propofol is flow dependent, so the liver blood flow plays a more significant role in drug elimination than the hepatic enzyme activity [19,20].

In this study we developed the PK/PD model in children undergoing different types of surgeries under propofol–fentanyl TIVA. Due to limited PK sampling the prior literature data obtained by Kataria et al. [14,21] were used to obtain information about the processes that were not supported by our data. The nonlinear mixed-effect approach was utilized to draw conclusions about PK/PD processes, especially to determine the link between the PK and PD in heterogeneous groups of children, which are encountered in real clinical settings.

Materials and methods

Patients

The study was approved by the local Bioethics Committee (Poznań University of Medical Sciences, Poland). A written informed consent was obtained from children and their parents.

Eighteen patients aged from 1 to 18 years, ASA status I–III, undergoing elective cardiac catheterization ($n = 11$), urological operation ($n = 4$) and inguinal herniotomy ($n = 3$) were enrolled into the study in two big centers of pediatric anesthesiology. All the patients were scheduled for procedures expected to last more than 1 h. Exclusion criteria included confirmed allergy to propofol, evidence of a severe failure of the hepatic, renal or endocrine system and ASA status IV or higher. Additionally, severe laboratory abnormalities, such as twice higher levels of bilirubin, aminotransferases, BUN and creatinine as well as hipoproteinemia and hypoalbuminemia and abnormal lipid profile excluded patients from the study. Table 1 summarizes the patient characteristics and laboratory data recorded throughout the study.

Table 1
Demographic data and physiological parameters of patients enrolled in the study. For continuous variables (systolic blood pressure, diastolic blood pressure, body temperature and heart rate) the median value of all records throughout the entire infusion were used for calculations.

Parameter, unit	Mean ± SD ($n = 18$); range
Age (year)	6.1 ± 4.4; 1.7–16
Body weight (kg)	24.9 ± 17; 10–70
Male/female	9/9
ASA I/ASA II/ASAIII	6/9/3
Total dose of propofol (mg)	293 ± 180; 48.4–739
Infusion duration (min)	50.3 ± 17.5; 16–73
Systolic blood pressure (mmHg)	101.3 ± 15.3; 75–158
Diastolic blood pressure (mmHg)	58.6 ± 22.1; 25–100
Heart rate (bpm)	97.1 ± 18.5; 61–177

Study design

One hour before arrival into the operating room all the patients received premedication with oral midazolam at age-dependent doses: 0.5 mg/kg (1–5 years or <25 kg b.w.), 0.3 mg/kg (≥6 years or 25–40 kg b.w.) and 7.5 mg for older children. In the operating room, before induction, a venous catheter was introduced to administer fluids, propofol and other drugs. Another catheter was placed into the contralateral arm for blood sampling after the induction of anesthesia. Standard noninvasive monitoring, including the heart rate (HR), non-invasive blood pressure (NBP), peripheral oxygen saturation (SpO_2), capnometry ($ETCO_2$) and temperature (TEMP), was performed for every patient. Additionally, before the induction of anesthesia and after the acceptance of the child Pediatric BisSensor leads (Aspect Medical Systems, GE) were applied to assess the depth of anesthesia. The skin on every patient's forehead was prepared according to the manufacturer's instructions. Propofol was administered with a standardized syringe pump Alaris TIVA (1000LBO1539 Iss2, CareFusion). All the children received 0.5 or 1.0 or 2.0% Propofol (Braun) at age-dependent doses. The scheme of TIVA-propofol administration included the loading dose followed by a continuous infusion at three decreasing dosage intervals. The induction of the children from group I (1–5 years) was performed at a dose of 4 mg/kg, and then it was followed by an infusion of 17 mg/kg/h at the first interval, 12 mg/kg/h at the second interval, and the final 10 mg/kg/h for the last 10 min, before the end of the procedure. The induction of the children from group II (6–12 years) was performed with propofol at a dose of 3 mg/kg, followed by an infusion of 15 mg/kg/h, and 10 mg/kg/h and 8 mg/kg/h for the last 10 min before the end of the procedure. Children from group III (older than 12 years) received a dose of 2 mg/kg of propofol, followed by 10 mg/kg/h, 8 mg/kg/h, and finally – 8 mg/kg/h, respectively. A single dose of mivacurium (0.2 mg/kg) was administered before the endotracheal intubation. A fentanyl dose of 1–1.5 μg/kg with the following repeated doses of 1/2 of the first one was routinely used to ensure proper analgesic effect during the procedure. The children were mechanically ventilated with a mixture of oxygen and air (40%/60%) to an end-tidal carbon dioxide tension ($ETCO_2$) between 35 and 45 mmHg. After the end of the procedure the infusion of propofol was stopped and the children were continuously monitored and given supplementary oxygen (100%) until they were awake and extubated.

All monitored data were continuously recorded at 5-min intervals, including the HR, SpO_2, $ETCO_2$, NBP, TEMP and BIS. At the beginning and at the end of propofol infusion the BIS values were recorded at 0.5 min intervals. There were nine venous blood samples (3 mL) collected from each patient during and after the