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Paediatrics

Predictive performance of eleven pharmacokinetic models for propofol infusion in children for long-duration anaesthesia

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Abstract

Background. Predictive performance of eleven published propofol pharmacokinetic models was evaluated for long-duration propofol infusion in children.
Methods. Twenty-one aged three–11 yr ASA I–II patients were included. Anaesthesia was induced with propofol or sevoflurane, and maintained with propofol, remifentanil, and fentanyl. Propofol was continuously infused at rates of 4–14 mg kg^{-1} h^{-1} after an initial bolus of 1.5–2.0 mg kg^{-1}. Venous blood samples were obtained every 30–60 min for five h and then every 60–120 min after five h from the start of propofol administration, and immediately after the end of propofol administration. Model performance was assessed with prediction error (PE) derivatives including divergence PE, median PE (MDPE), and median absolute PE (MDAPE) as time-related PE shift, measures for bias, and inaccuracy, respectively.
Results. We collected 85 samples over 270 (130) (88–545), mean (SD) (range), min. The Short model for children, and the Schüttler general-purpose model had acceptable performance (–20%≤MDPE ≤ 20%, MDAPE ≤ 30%, –4% h^{-1} ≤ divergence PE ≤ 4% h^{-1}). The Short model showed the best performance with the maximum predictive performance metric. Two models developed only using bolus dosing (Shangguan and Saint-Maurice models) and the Paedfusor of the remaining nine models had significant negative divergence PE (≤–6.1% h^{-1}).
Conclusions. The Short model performed well during continuous infusion up to 545 min. This model might be preferable for target-controlled infusion for long-duration anaesthesia in children.

Key words: paediatrics; pharmacokinetics; propofol

Target-controlled infusion (TCI) with propofol is frequently used for paediatric anaesthesia.[1–3] When using TCI in children, the hypnotic component of anaesthesia can be titrated to a specific plasma concentration (Cp). Intermittent measurement of propofol plasma concentration could be applied,[4] however, no practical and robust technology is currently available to measure real-time plasma concentrations of propofol during anaesthesia. Thus predicted propofol concentrations using incorporated pharmacokinetic (PK) models are used during TCI.

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Editor's key points

- Pharmacokinetic models are useful in predicting plasma concentrations for target-controlled infusion (TCI), but the various models differ in their predictive performance.
- The performance of 11 pharmacokinetic models was evaluated for propofol TCI in 21 children undergoing long-term infusions.
- Two of the models had acceptable performance in predicting measured plasma propofol concentrations, and are preferred for use in long duration propofol TCI.

The accuracy of TCI depends highly on the accuracy of the applied PK model to predict the time course of the plasma concentration and to control infusion rates. Of particular importance for long-duration anaesthesia is the possibility for systematic changes in PK model predictive performance over time. Predictive performance of a PK model early in a patient could differ from those later in the same patient and give the clinician a false impression of stability (or instability) of anaesthetic conditions. Deterioration of predictive performance of a PK model over time might result in unrecognised under- or over-dosing of propofol. This might lead to adverse effects such as intraoperative awareness, delayed emergence from anaesthesia, or misinterpreted haemodynamic instability. Previously, predictive performances of paediatric PK models have only been evaluated for limited durations of propofol infusion up to three h. One study[5] has assessed eight models[6–13] during propofol infusion over 99 (31) min (mean (SD)) and over two h after surgery in three-26 month children using arterial samples. Another study[11] evaluated eight models[6–10 14–16] up to 45 min after start of propofol infusion using TCI in children four–11 yr of age using venous samples. Although the Paedfusor[6] and Marsh (for adults) models were simultaneously assessed in children nine–17 yr old for up to six h,[17] the performance of published paediatric PK models for long-duration anaesthesia has not been evaluated.

The aim of the study was to examine the prediction accuracy of published propofol PK models for anaesthesia of > two h duration in children. The hypothesis was that PK models can predict propofol Cp for long-duration anaesthesia with acceptable prediction stability judged on the following three criteria: divergence prediction error (PE) between –4% h^{-1} and 4% h^{-1} with median prediction error (MDPE) between –20% and 20% and median absolute prediction error (MDAPE) < 30%.

Methods

This prospective observational study was approved by the institutional research and ethics committee of Chiba Children's Hospital (Chiba, Japan). After obtaining written informed consent from the parents of each paediatric patient, we enrolled patients of three to 11 yr of age, ASA physical status I or II, and undergoing tympanoplasty, cranioplasty, cleft lip correction, or orthopaedic surgery. We included patients with expected anaesthesia times of > two h. Exclusion criteria included morbid obesity, congenital heart disease, liver or renal dysfunction, neurological disorder, and allergy to soybeans or eggs.

Clinical protocol

Patients were not premedicated and were monitored using ECG, non-invasive bp, pulse oximetry, and capnography. Anaesthesia was induced with propofol, remifentanil, and fentanyl via a peripheral i.v. line, or with sevoflurane and nitrous oxide in oxygen via face mask. After rocuronium was administered, the trachea was intubated. Anaesthesia was maintained with propofol, remifentanil, and fentanyl. Propofol was continuously infused at rates between four and 14 mg $kg^{-1} h^{-1}$ after an initial bolus of 1.5 or 2.0 mg kg^{-1}. Remifentanil infusion was started at a rate of 0.5 μg $ml^{-1} min^{-1}$ and fentanyl 1–2 μg kg^{-1} was given as an initial bolus. Infusion rates of propofol and remifentanil were adjusted and additional doses of fentanyl was given as required.

Sample acquisition and drug assay

For blood sampling, we used a 22 gauge peripheral venous catheter at a limb on the opposite side of the i.v. line for propofol administration. Venous blood samples (0.5 ml each) were obtained every 30–60 min for up to five h and every 60–120 min after five h from the start of propofol administration during the maintenance of anaesthesia, and immediately after the end of propofol administration. After a change of dose rate of propofol, we avoided drawing blood samples for five min. Blood samples were centrifuged and plasma was kept at −30 °C until assayed. Venous plasma concentrations (Cp) of propofol were determined using high-performance liquid chromatography.[18]

PK models studied

We selected eleven published PK models of propofol; nine models for children (Paedfusor,[6] Kataria,[7] Marsh,[8] Short,[9] Rigby-Jones,[10] Coppens[11], Saint-Maurice[12], Shangguan[14], and Murat[13] models); and two general-purpose models for children and adults (Schüttler[15] and Eleveld[19] models). All were developed as three compartment models. The pharmacokinetic parameter sets applied in the present study and the background of the PK model development including patient age, dose regimen of propofol, and blood sampling are shown in Tables 1 and 2. The detailed background of the Paedfusor model including subject characteristics, dose regimen of propofol, and blood sampling have not been described.[6 15 20] The range of age in subjects was limited, (i.e. four to seven, four to seven or one to three yr), for development of the Short, Saint-Maurice, and Murat models, respectively. Only bolus dosing was performed for the Saint-Maurice, Shangguan, and Murat models. Arterial blood samples were obtained for the Rigby-Jones and Shangguan models, both arterial and venous samples for the Schüttler and Eleveld models, and venous samples for the remaining seven models. For the Marsh and Short models, external evaluation was performed to confirm robustness of the models using data which were excluded from the model development. Details of model development can be found in the original articles.

Model evaluation

A goodness-of-fit plot was produced for each pharmacokinetic model. The plot depicted prediction error (PE) as the y-axis against time as the x-axis, in individuals to clarify the time-related bias of the prediction. For each measurement of propofol Cp, PE (%) was determined as (measured Cp – predicted Cp)/predicted Cp × 100, where predicted Cp was calculated using the assessed PK model. When an applied model perfectly predicts Cp (i.e. the predicted Cp is equal to the measured Cp), then the corresponding PE value is 0%.