

Performance evaluation of paediatric propofol pharmacokinetic models in healthy young children

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Editor's key points

- Total i.v. anaesthesia using target-controlled infusion of propofol is widely used, but the relative performance of available pharmacokinetic models in young children is unclear.
- Eight models were tested in their ability to predict arterial propofol concentrations during infusion in young children.
- Six of eight models performed well, but most underestimated initial propofol concentration.

Background. The performance of eight currently available paediatric propofol pharmacokinetic models in target-controlled infusions (TCIs) was assessed, in healthy children from 3 to 26 months of age.

Methods. Forty-one, ASA I–II children, aged 3–26 months were studied. After the induction of general anaesthesia with sevoflurane and remifentanyl, a propofol bolus dose of 2.5 mg kg⁻¹ followed by an infusion of 8 mg kg⁻¹ h⁻¹ was given. Arterial blood samples were collected at 1, 2, 3, 5, 10, 20, 40, and 60 min post-bolus, at the end of surgery, and at 1, 3, 5, 30, 60, and 120 min after stopping the infusion. Model performance was visually inspected with measured/predicted plots. Median performance error (MDPE) and the median absolute performance error (MDAPE) were calculated to measure bias and accuracy of each model.

Results. Performance of the eight models tested differed markedly during the different stages of propofol administration. Most models underestimated propofol concentration 1 min after the bolus dose, suggesting an overestimation of the initial volume of distribution. Six of the eight models tested were within the accepted limits of performance (MDPE < 20% and MDAPE < 30%). The model derived by Short and colleagues performed best.

Conclusions. Our results suggest that six of the eight models tested perform well in young children. Since most models overestimate the initial volume of distribution, the use for TCI might result in the administration of larger bolus doses than necessary.

Keywords: anaesthetics i.v., propofol; children; drug infusion systems; pharmacokinetics

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Total i.v. anaesthesia (TIVA) with propofol has gained popularity in recent years as an alternative to inhalation anaesthesia in children.^{1–4} The introduction of target-controlled infusion (TCI) systems into clinical practice and the development of paediatric propofol pharmacokinetic (PK) models^{1 2 5} have made i.v. anaesthesia more attractive. Clinical advantages of TIVA compared with inhalation anaesthesia have also been reported.^{6 7}

Current paediatric propofol PK models described by Saint-Maurice and colleagues,⁸ Marsh and colleagues⁹ (hereafter referred to as the 'Marsh paediatric' model to avoid confusion with the adult model), Kataria and colleagues,¹⁰ Short and colleagues,¹¹ Murat and colleagues,¹² Rigby-Jones and colleagues,¹³ Absalom and colleagues (Paedfusor),⁵ and Coppens and colleagues¹⁴ were derived with data from heterogeneous paediatric populations, with ages ranging from the neonatal period to 16 yr, and with high variable health

condition (healthy to critically ill). Most models only use bodyweight as a covariate. However, other factors such as comorbidity and age can significantly influence PK parameters during model development, and can thus influence the predictive capacity of these models when applied to different populations from those in which they were derived.

Rational implementation of TCI and TIVA in children should be based on rigorous validation of available paediatric PK models, but such studies are scarce.^{1 3} In a prospective study, the Paedfusor model showed very good predictive capability in children between 1 and 15 yr.¹⁵ Most children in that study, however, had significant cardiac problems, thus making it difficult to extrapolate those results to a healthy population. In another study in healthy children between 6 and 13 yr, Rigouzzo and colleagues¹⁶ found that the PK predictive performance of the Kataria and colleagues¹⁰ and Schnider and colleagues¹⁷ models was poor

and showed wide interindividual variability. Despite this, the authors found that the Schnider and colleagues' adult model better characterized the clinical effect time profile of propofol in prepubertal children compared with the Kataria and colleagues, Marsh paediatric,⁹ and Schüttler and Ihmsen¹⁸ models. However, it is difficult to recommend the Schnider model for use in children, given the limited age range and the fact that measured plasma propofol concentrations were on average 50% greater than predicted. In this situation, the reasonable prediction of the time course of clinical effects by definition must have involved counter-balanced PK and pharmacodynamic (PD) errors.

On the basis of current data, it is not clear which model should be applied to clinical practice in children older than 3 yr (or indeed whether an altogether new model is required). With regard to children younger than 3 yr, there are no data on which to inform practice, since none of the currently available paediatric propofol models has been prospectively assessed in this age group. To define and validate a complete PK and PD model, a reliable and objective measure of clinical effect is required. It is known that in small children, younger than 1 yr of age, currently available objective measures of hypnotic effect, such as the bispectral index and entropy, perform poorly.¹⁹

Although existing technology is insufficient for defining a full PK/PD model, we believe that there is still value in at least validating PK models in small children, since TCI systems can still be used successfully in clinical practice in plasma-targeted mode (as occurred for several years in the 1990s with adult TCI systems for propofol).²⁰ Thus, the aim of the current study was to prospectively assess the performance of eight currently available paediatric propofol PK models in healthy children from 3 months to 3 yr of age.

Methods

With approval from the institutional research and ethics committee (School of Medicine, Clínica Alemana, Universidad del Desarrollo, Santiago, Chile), and after obtaining written informed consent from the parents, 41 children aged 3–26 months were studied. All children were ASA class I or II, and were undergoing cleft lip and cleft palate surgery. Patients with respiratory, renal, hepatic, or endocrine function deficiencies or with a family history of allergic reactions to any component of propofol were excluded.

Study protocol

Subjects were not premedicated and were monitored with ECG, and non-invasive arterial pressure. Anaesthesia was induced with 6% sevoflurane in oxygen. A 22 G peripheral i.v. line and a 22 G radial artery Sp_O₂ line were placed. Remifentanyl infusion was started at a rate of 0.2 µg kg⁻¹ min⁻¹ and adjusted during surgery to maintain immobility and haemodynamic stability (heart rate and arterial pressure) within 20% of baseline values. After securing the airway with a tracheal tube, patients were mechanically ventilated. Sevoflurane administration was then terminated, and when

end-tidal concentrations decreased to ≤0.5 MAC for 5 min, a bolus dose of propofol 2.5 mg kg⁻¹ followed by an infusion of 8 mg kg⁻¹ h⁻¹ was given and maintained throughout surgery using a Base A Fresenius pump (Fresenius Vial Infusion Systems, Brézins, France). Arterial blood samples of 2 ml were collected at 1, 2, 3, 5, 10, 20, 40, and 60 min post-bolus, at the moment the infusion was stopped (end of surgery), and at 1, 3, 5, 30, 60, and 120 min thereafter. The samples were centrifuged, and red blood cells and plasma were separated.

Propofol assay

Blood samples were kept on ice and centrifuged within the first 2 h after collection. Plasma samples were then stored at –20°C until analysis. High-performance liquid chromatography to measure propofol plasma concentrations was performed using the method described by Seno and colleagues.²¹ The calibration curve was linear within 0.1–10 µg ml⁻¹, with a correlation coefficient (*r*²) of 0.9993. The plasma propofol lower limits of detection and quantification were 0.01 and 0.1 µg ml⁻¹, respectively. Intra-day precision (CV%) at 0.1, 0.3, 0.75, 1.25, 2.5, 5, and 10 µg ml⁻¹ were 1.7%, 4.8%, 4.0%, 2.8%, 1.9%, 1.9%, and 1.3%, respectively (*n*=6). Inter-day assay precision (CV%) at 0.1, 1, 3, and 7.5 µg ml⁻¹ were 6%, 3%, 5%, and 3.5%, respectively (*n*=20).

Data analysis

Estimations of the predicted propofol plasma concentrations (C_p) for each model were performed by simulation using each individual weight and dose profile. Simulations were performed with NONMEM VI (Globo-Max LLC, Hanover, MD, USA).²² The predicted C_p values were then compared with the measured C_p values. Model performance was evaluated using the methods recommended by Varvel and colleagues.²³ For each sample, performance error (PE), median performance error (MDPE), and median absolute performance error (MDAPE) were calculated. The PE for each sample was obtained using the predicted C_p and the measured C_p according to the following equation:

$$PE(\%) = \frac{C_p \text{ measured} - C_p \text{ predicted}}{C_p \text{ predicted}} \times 100 \quad (1)$$

The series of PEs were then used to calculate, for each subject and for the entire group, the MDPE and the MDAPE of each model. The MDPE and MDAPE were calculated for each subject *i*, having *N_i* blood samples as follows:

$$MDPE_i = \text{Median} \{PE_{ij}, j = 1, \dots, N_i\} \quad (2)$$

$$MDAPE_i = \text{Median} \{|PE_{ij}|, j = 1, \dots, N_i\} \quad (3)$$

The MDPE represents the median bias of the model (a positive value means model underestimation, a value of 0 means no bias, and a negative value means model overestimation). The MDAPE represents the median accuracy of the prediction (a value of 0 means perfect accuracy). On the

basis of previous studies assessing PK models performance under different administration schemes, we considered acceptable model performance, if MDPE was between -20% and 20% and if MDAPE was $<30\%$.^{24 25}

Diagnostic plots showing the time profile of measured Cp/predicted Cp were used to visually inspect model performance throughout the entire sampling period (bolus dose, constant infusion, and recovery).

Statistical analysis

Normality of data was tested with the Shapiro test. Non-parametric multiple comparisons of error indices between models were performed with the multiple Behrens–Fisher test. Data are shown as mean (sd). A *P*-value of <0.05 was considered significant. Statistical analyses were done using R version 2.8.1 (<http://www.R-project.org>).

Results

A total of 41 subjects, 18 girls and 23 boys, were studied; their general characteristics are shown in Table 1. No haemodynamic events requiring vasoactive drug administration were reported. The average duration of anaesthesia was 99 (31) min. Mean remifentanyl consumption throughout the study period was 0.26 (0.07) $\mu\text{g kg}^{-1} \text{min}^{-1}$.

A total of 543 arterial blood samples were collected for the analysis. The time profile of the measured propofol concentrations is shown in Figure 1. Predictive performance indices of the tested models are shown in Table 2. MDPE

(%) and MDAPE (%) ranged from -20% to 36% and from 18% to 40% , respectively. On the basis of the criteria used to define an adequate model performance (MDPE $<20\%$ and MDAPE $<30\%$), six of the eight model tested were within the accepted limits of performance. In the model derived by Short and colleagues, the inter-quartile ranges of MDPE and MDAPE fell also within these accepted limits. The time profile of the performance indices in each model tested is shown in Figure 2. Three PK models (Rigby-Jones and colleagues, Marsh paediatric, and Coppens and colleagues) showed median negative bias values (i.e. overestimation of plasma concentrations) throughout the study period; most models showed an overall tendency to underestimate measured concentrations (positive bias). In general, positive bias was observed 1 min after the bolus dose and during the end stages of the constant infusion period. In contrast, negative bias was commonly observed shortly after the bolus dose (2–10 min) and after stopping propofol infusion (Table 3). No correlation between age and MDPE (%) or MDAPE (%) was observed.

Table 4 shows the PK parameters estimated by all models tested for a 10 kg 1-yr-old patient. Figure 3 shows the propofol concentration–time profiles predicted by all tested models after a typical bolus plus infusion scheme in a 10 kg 1-yr-old patient.

Discussion

On the basis of the criteria used to define adequate model performance, the predictive performance of six of the PK models tested was within the acceptable limits in healthy young children between 3 and 26 months of age. It should be noted, however, that the performance of these models differed markedly during different stages of propofol administration (bolus dose, constant rate infusion, and recovery).

In the early phase after bolus dose administration, all models except the Marsh paediatric and Coppens and colleagues' models underestimated the propofol concentration. Soon after a bolus dose, the peak concentration depends strongly on the initial volume in which the dose is distributed, while the concentration profile soon after the peak depends strongly on rapid redistribution from that volume.²⁶ This suggests that, with the exception of the Marsh paediatric and Coppens and colleagues' models, the size of the initial volume of distribution (central compartment, or V_1) was too large for the studied children. The potential clinical relevance of this is that if these models are used to control TCI systems, then for any given target concentration, the size of the initial bolus is likely to be excessive. In addition, a recent review by Constant and Rigouzzo³ suggest that current paediatric models poorly characterize the initial phase of distribution and therefore are unable to adequately predict the clinical effect time profile of propofol in children when linked to PD parameters.⁹

In our study, the most probable reason for the observed central volume overestimation is that most paediatric models were derived from venous samples. PK models

Table 1 General characteristics of subjects. Values are mean (range)

Age (months)	9.9 (3.2–26)
Weight (kg)	8.2 (5.2–11.4)
Height (cm)	68.5 (57–79)

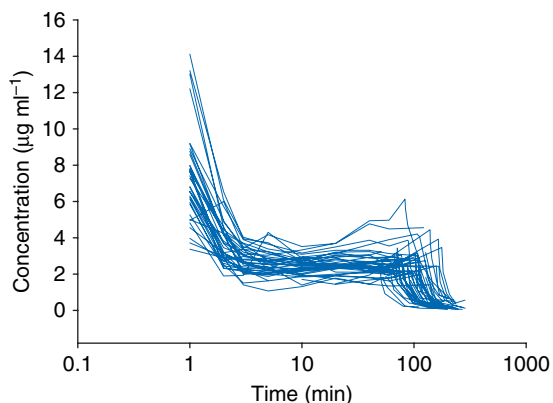


Fig 1 Time profile of measured arterial propofol concentrations in all subjects.

Table 2 Performance indices of the paediatric models tested. Values are median (25th; 75th percentiles); non-parametric multiple comparisons performed with the multiple Behrens–Fisher test. * $P < 0.01$ compared with the lowest error model: MDPE (%), compared with the Saint-Maurice and colleagues' model; MDAPE (%), compared with the Short and colleagues' model

	Short	Rigby-Jones	Coppens	Kataria	Paedfusor	Marsh	Saint-Maurice	Murat
MDPE (%)	5.44 (-9.3; 15.4)	-7.43 (-20.4; 1.9)	-16.47* (-23.4; -5.6)	8.03 (-2.8; 23.1)	4.97 (-8.0; 21.2)	-20.12* (-28.4; -8.9)	-0.02 (-6.2; 17.8)	35.65* (23.9; 54.9)
MDAPE (%)	18.21 (14.8; 29.2)	20.75 (16.2; 30.3)	21.01 (15.3; 29.7)	21.11 (16.7; 32.7)	22.83 (17.6; 32.5)	23.55* (19.6; 32.4)	25.07* (20.2; 34.6)	40.07* (35.7; 54.9)

derived with venous samples instead of arterial samples estimate larger central volumes due to the lower drug concentration observed in venous blood during the early and intermediate phases of drug administration.^{26–28} Although the Rigby-Jones and colleagues' model¹³ was derived with arterial samples, it also underpredicted the initial concentrations after the bolus dose. The reason for this may be found in two aspects of their study protocol. The first is that it involved a constant infusion scheme, without a bolus, which limits the accuracy of the estimate of V_1 .¹⁷ The second is that no early arterial samples were acquired, and this too limits the ability to adequately describe the initial phase of propofol distribution.

In adult patients, propofol concentrations decrease rapidly after a bolus dose as a result of fast redistribution.^{17 18} Compared with adults, children have even higher weight proportional propofol clearance and distribution volumes.^{9 18} After an infusion, the rate of decline in plasma concentration is more complex. It is a polyexponential process since it depends on metabolic clearance and also slow and fast re-distribution to and from the central compartment. The overall contribution of the different exponential processes just described depends on the duration of infusion for drugs such as propofol in which the kinetics are context-sensitive. In our study, the infusion duration lasted a mean of 99 min. After the infusion was terminated, the observed rate of decay was in general faster than that predicted by the tested models. This faster decay is in accordance with studies showing very rapid overall propofol clearance in infants compared with neonates and older children.^{29 30 31} Our findings contrast with those of Absalom and colleagues¹⁵ who observed slower rates of decay after an infusion than that predicted by the Paedfusor model in children aged 1–15 yr. In that study, however, patients selected were undergoing cardiac surgery or catheterization and therefore, most probably had decreased cardiac output, which could limit hepatic flow (and thus metabolic clearance) and redistribution.¹³

Higher than expected clearance in small children might also be due to other factors such as the increased relative liver size observed at this age, and the activity of multiple cytochrome P450 enzyme pathways that clear active propofol by hydroxylation.¹ It appears that age-related changes in clearance might be better described by allometric scaling rather than linear scaling according to bodyweight, and so future incorporation of allometric scaling and the incorporation of clearance maturation and organ function as model covariates should improve predictions of clearance in children.^{1 32 33}

Wide inter-individual PK variability normally seen in children, especially during the first 2 yr of life,^{1 3} was also observed in our results, where propofol concentrations measured after similar milligram per kilogram dose schemes were highly variable between patients. In our study, the model derived by Short and colleagues using healthy Chinese children between 4 and 10 yr during TCI propofol administration performed best. In terms of bias and precision, the median values and the inter-quartile ranges

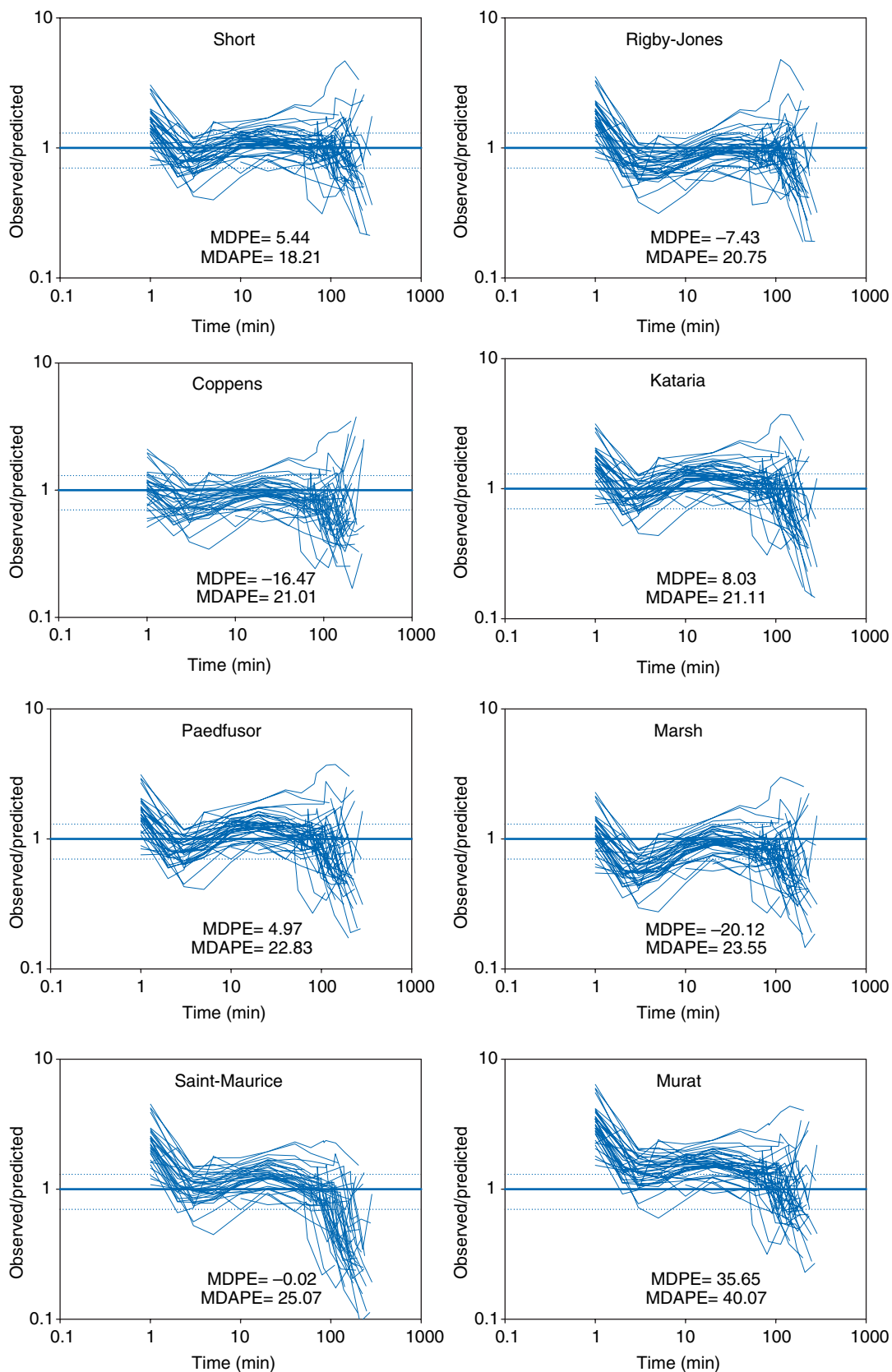


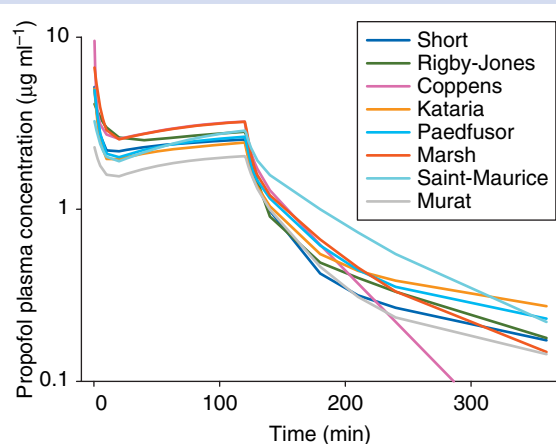
Fig 2 Time profile of the observed/predicted propofol plasma concentration (C_p) for the eight PK models. Each line represents one subject. The dotted line indicates an acceptable range of measured/predicted C_p . The bold horizontal line indicates perfect prediction capacity.

Table 3 Performance indices of the paediatric models tested according to the anaesthesia period

	Short	Rigby-Jones	Coppens	Kataria	Paedfusor	Marsh	Saint-Maurice	Murat
MDPE								
Bolus	6	6	-13	13	6	-24	41	96
Infusion	8	-7	-11	17	18	-12	12	44
Recovery	-10	-17	-32	-16	-22	-33	-40	-5
MDAPE								
Bolus	29	41	23	30	30	36	46	95
Infusion	16	15	15	19	18	16	18	44
Recovery	27	30	36	31	33	36	43	31

Table 4 PK parameters estimated with each paediatric model for a 10 kg 1-yr-old patient (weight is the only covariate of the selected models)

	Short	Rigby-Jones	Coppens	Kataria	Paedfusor	Marsh	Saint-Maurice	Murat
V1 (litre)	4.32	5.84	1.74	4.40	4.58	3.43	7.22	10.3
V2 (litre)	5.59	13.60	2.34	7.00	9.50	8.9	17.8	9.7
V3 (litre)	34.56	159.7	9.51	57.00	58.20	20.3	84.0	60.87
CL (litre min ⁻¹)	0.42	0.30	0.39	0.37	0.35	0.34	0.31	0.49
Q2 (litre min ⁻¹)	0.61	0.16	1.02	0.65	0.52	0.29	0.62	0.67
Q3 (litre min ⁻¹)	0.17	0.13	0.33	0.27	0.19	0.07	0.11	0.20

**Fig 3** Time profile of plasma concentrations predicted by all tested models after a bolus dose of propofol 2.5 mg kg⁻¹ followed by an infusion of 8 mg kg⁻¹ h⁻¹ for 2 h in a 10 kg subject.

fell within criteria used to define adequate model performance. As a result, this model, characterized by relatively small volumes of distribution but generally larger elimination and redistribution clearance rates, showed more stable performance throughout the study period.

PK parameters can be markedly biased if derived from studies with relatively short sampling periods. In general, the longer the infusion and the sampling period, the better the estimate of volume of distribution at steady state (i.e. V1+V2+V3) and metabolic clearance.³⁴ Likewise, the

information yield of prospective validation studies with short sampling periods can be limited. In our study, performance of the models was assessed during relatively short infusion schemes and recovery periods. This study design probably masked relevant discrepancies between models that might have been evident with a longer observation period. It is therefore possible that if we had measured the propofol recovery profile for a longer period of time, those models derived using long sampling periods (12–24 h)^{8 12 13} would have shown better prediction compared with those derived after short infusion schemes.

Differences in assay methodology between our study and those used during model development studies should also be considered. Most of the models tested were completely^{8 9 11–13} or partially⁵ developed with whole-blood propofol assays, whereas we measured plasma propofol concentrations. Plasma propofol concentrations can be 30% higher than whole-blood concentrations, if plasma is separated immediately after collection, and 5–10% higher, if samples are stored for 1 h before centrifugation.³⁵ Since we centrifuged 1–2 h after blood sampling, it is expected that plasma propofol concentrations would be 5–10% higher than whole-blood measurements. Given the possibility of non-linear kinetics, the mode of propofol administration and the dose range from which the models were derived are other possible sources of differences in model performance. Models based on sedative dose schemes perform poorly if tested at higher dose ranges and vice versa. Dose schemes used in developing the currently tested models were highly variable, ranging from low-dose constant infusion schemes¹³ of 4 mg kg⁻¹ h⁻¹ to relatively high TCI ranges⁹ of 12–14 µg ml⁻¹.

Schnider and colleagues¹⁷ showed that a propofol model derived from infusion data poorly predicted observations after a bolus dose. Similarly, Vuyk and colleagues³⁶ showed that during TCI administration, propofol PK parameters derived from bolus data resulted in worse prediction than models derived with infusion schemes. In agreement with these studies, our results showed the highest MDAPE in the Murat and colleagues' and Saint-Maurice and colleagues' models which were derived exclusively from bolus data. In general, these two models predict higher central volumes than the other tested models, which probably partly results from the erroneous assumption of instantaneous mixing in the central compartment after a bolus dose.³⁷ In addition, underestimation of metabolic clearance in models derived with bolus data might result from transient cardiovascular depression and reduced liver blood flow caused by the bolus. Reduced clearance, however, is only apparent in the Saint-Maurice and colleagues' model, derived after a bolus dose of 2.5 mg kg⁻¹ in healthy children aged 4–7 yr. In the Saint-Maurice and colleagues' model, the value estimated for this parameter is comparable with that estimated by Rigby-Jones and colleagues in critically ill children. In contrast to this hypothesis, a high metabolic clearance is estimated by the Murat and colleagues' model, despite the fact that the study involved a higher bolus dose of propofol (4 mg kg⁻¹) in children aged 1–3 yr with minor burns. Metabolic clearance estimation depends heavily on the timing of the last blood samples for propofol assays.³² Since the last samples in the Murat study were taken 8 and 12 h after the bolus dose, it seems unlikely that transient haemodynamic changes after a bolus could have significantly affected this parameter. Most probably, the higher clearance observed in the Murat and colleagues' model compared with the Saint-Maurice and colleagues' model comes from the longer sampling period of the latter study where the last samples were taken 12 and 24 h after the bolus dose. Other factors to be considered in the higher clearance of the Murat and colleagues' study are the younger age group (1–3 yr) relative to the Saint-Maurice and colleagues' study (4–7 yr) and the inclusion of burns patients. Increased cardiac output, with a concomitant increase in the liver and kidney blood flow, can be observed in burned patients during the hypermetabolic recovery phase.³⁸ These factors highlight the difficulty of comparing individual parameter values between the models tested when the underlying populations and study design conditions are very different.

In adult patients, administration of 2% sevoflurane has been shown to significantly increase propofol plasma concentrations.³⁹ In addition, a significant increase in propofol concentrations has also been observed after the administration of remifentanyl 1.0 µg kg⁻¹ min⁻¹ in adult patients.⁴⁰ Although we used somewhat lower doses of sevoflurane and remifentanyl, a possible PK interaction of propofol with these two drugs cannot be ruled out.

From our results, it is not possible to understand the exact influence of all sources of variability observed. Discrepancies between models can probably only be adequately explained

if a new integrated PK model is derived using data of different propofol PK studies in children and adult patients. In the meantime, the overall poor predictive ability showed by most models shortly after the bolus dose and during moments where rapid changes in propofol concentrations occur support the use of PD feedback with EEG monitors to achieve better control of the effect, at least in children older than 1 yr where these monitors have shown better performance.^{1 3 19}

We conclude that the global performance of six currently available propofol PK models was good when used in children aged 3–26 months. Although our results suggest that these models could perform well when used to control TCI in young children, the underprediction of concentrations soon after the initial bolus suggests that if used for TCI, these models could result in administration of larger initial bolus doses than necessary.

Conflict of interest

None declared.

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