

Pharmacokinetics of Propofol Infusions in Critically Ill Neonates, Infants, and Children in an Intensive Care Unit

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Background: Propofol is a commonly used anesthetic induction agent in pediatric anesthesia that, until recently, was used with caution as an intravenous infusion agent for sedation in pediatric intensive care. Few data have described propofol kinetics in critically ill children.

Methods: Twenty-one critically ill ventilated children aged 1 week to 12 yr were sedated with 4–6 mg · kg⁻¹ · h⁻¹ of 2% propofol for up to 28 h, combined with a constant morphine infusion. Whole blood concentration of propofol was measured at steady state and for 24 h after infusion using high-performance liquid chromatography.

Results: A propofol infusion rate of 4 mg · kg⁻¹ · h⁻¹ achieved adequate sedation scores in 17 of 20 patients. In 2 patients the dose was reduced because of hypotension, and 1 patient was withdrawn from the study because of a increasing metabolic acidosis. Mixed-effects population models were fitted to the blood propofol concentration data. The pharmacokinetics were best described by a three-compartment model. Weight was a significant covariate for all structural model parameters; Cl, Q₂, Q₃, V₁, and V₂ were proportional to weight. Estimates for these parameters were 30.2, 16.0, and 13.3 ml · kg⁻¹ · min⁻¹ and 0.584 and 1.36 l/kg, respectively. The volume of the remaining peripheral compartment, V₃, had a constant component (103 l) plus an additional weight-related component (5.67 l/kg). Values for Cl were reduced (typically by 26%) in children who had undergone cardiac surgery.

Conclusions: Propofol kinetics are altered in very small babies and in children recovering from cardiac surgery. Increased peripheral distribution volume and reduced metabolic clearance following surgery causes prolonged elimination.

OPIOIDS, benzodiazepines, and chloral hydrate are commonly used for the sedation of critically ill children on the pediatric intensive care unit, but all have side effects, such as respiratory depression, delayed recovery from relative overdose, drug tolerance, and withdrawal phe-

nomena.^{1,2} Propofol has been used to provide smooth and predictable sedation in children,^{3,4} but recently its use has been contraindicated because of concerns that its use may be associated with increased mortality⁵ and that it can cause a syndrome characterized by bradycardia, rhabdomyolysis, metabolic acidosis, hypotension, and death.^{6–8} While there are limited data on the kinetics of propofol in well children,^{9–11} even less is known of the kinetics in critically ill neonates and infants.¹² We hypothesized that the pharmacokinetics of propofol in neonates and young babies might be substantially altered compared with older infants and children and that these differences may be clinically important. We therefore wished to accurately describe the pharmacokinetics of propofol when given as a sedative infusion to very young critically ill children, including those with low cardiac outputs. We also wished to relate these data to factors such as age, weight, gender, infusion duration, and clinical diagnosis.

Materials and Methods

After obtaining local ethics committee approval and written informed parental consent, we studied 21 neonates and children up to the age of 12 yr requiring sedation and ventilation following cardiac surgery or for single organ failure. Cardiac surgery patients were excluded from the study if prolonged postoperative ventilation or major inotropic support was anticipated. Sedation was achieved with an infusion of 2% propofol combined with a background infusion of morphine. The aim was to provide a constant morphine infusion rate while an individualized infusion rate of propofol was delivered to achieve target sedation scores. Sedation scoring was performed hourly using an observational pain scale¹³ modified for intensive care (table 1),¹⁴ with a range of scores from 0 to 8. Adequate sedation was considered to be a score of 2–4, which is consistent with the degree of sedation normally achieved in the pediatric intensive care unit.

Patients undergoing cardiac surgery were anesthetized with isoflurane and fentanyl (50 µg/kg). Morphine sulfate (0.5–1 mg/kg) was added to the cardiomyotomy reservoir before commencing cardiopulmonary bypass, and isoflurane was administered *via* the sweep gases. Propofol infusion commenced at 4 mg · kg⁻¹ · h⁻¹ without an initial bolus, after cardiopulmonary bypass had been discontinued or on returning to the pediatric intensive care unit. In all other children, propofol was

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Table 1. Sedation Score for Ventilated Non-Paralyzed Children

	0	1	2
Facial expression	No movement, asleep	Alert, relaxed expression	Anxious, frown, crumpled face, silent cry
Body movement	No movement, asleep	Some movement, relaxed position	Jerky, uncoordinated, arching
Agitation	No movement, asleep	Some agitation, can be comforted	Cannot be comforted
Ventilation	No respiratory effort	Triggering, synchronizing	Asynchrony

introduced as an infusion, either after induction of anesthesia-sedation with another agent or to replace a previous sedative agent that had been considered unsatisfactory. Morphine was commenced at $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Sedation was maintained with $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol and $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ morphine if sedation scores remained within the target range. Undersedation was treated with a bolus injection of $20 \mu\text{g}/\text{kg}$ morphine and the morphine infusion rate was increased to $40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ if sedation remained unsatisfactory. Morphine boluses were also given prior to tracheal suctioning and physiotherapy. Propofol was increased to $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and then to a maximum of $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ if target sedation scores were not achieved with $40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ morphine. No propofol boluses were given.

Arterial blood pressure was monitored invasively in all cases. Hypertension was treated in the same way as undersedation, or by adjusting inotropes, according to clinical impression. Hypotension was defined as a persistent reduction in mean blood pressure by more than 20%. If judged to be caused by poor cardiac performance (increased arterial lactate and decreased venous saturations), it was treated with appropriate inotropes. Initial support was with dopamine infused at $5\text{--}10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with epinephrine as a second agent. Hypotension associated with low central venous pressure was treated with volume replacement, initially $20 \text{ ml}/\text{kg}$ crystalloid. If hypotension was considered to result from oversedation, the rate of propofol infusion was reduced in increments of $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ to a minimum of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Propofol was discontinued for weaning or if sedation was required for more than 24 h when it was replaced by another sedative agent. Triglyceride and cholesterol levels were determined before commencing and immediately on stopping the infusion. No child received parenteral nutrition during the study. Laboratory investigations were routinely performed for urea, electrolytes, liver function tests, lactate, and acid-base status before, during, and after the propofol infusion.

Propofol Analysis

Propofol was infused at constant rate for 4 h or more in each patient before the infusion was withdrawn. Once target sedation scores were achieved, arterial blood samples were obtained hourly. The purpose of these samples was to establish steady state blood propofol concentrations during optimal sedation, as well as to

contribute to the pharmacokinetic model fitting. After the propofol infusion was withdrawn, arterial blood samples were taken immediately and at 5, 10, 15, and 30 min and at 1, 2, 3, 6, 12, and 24 h, and 48 h when possible. Blood samples were collected in oxalate tubes and stored at 4°C until analysis.

Propofol was extracted from whole blood using a solid phase extraction procedure¹⁵ and analyzed by high-performance liquid chromatography.¹⁶ The high-performance liquid chromatography assay was stability indicating and had proven linearity. Intraday precision was 6.3% and 11.8% at 100 and 1,000 ng/ml, respectively ($n = 5$). Interday precision at 100, 500, 1,000, and 2,000 ng/ml was less than 8% ($n = 5$). The limit of quantification was 2 ng/ml.

Pharmacokinetic Model

Mixed-effects population models were fitted to the propofol concentration data. The program NONMEM V was used, running on a SUN Enterprise computer with a Solaris operating system.¹⁷ The mixed-effects approach defines a single basic model of typical values (population means) for the pharmacokinetic parameters. Variations in each individual from the basic model were defined by the use of a variable number of additional, user-defined "interindividual variability parameters," each defining a degree of variability in one or more of the basic parameters. For instance, clearance was modeled as:

$$\text{Cl} = \text{Cl}_{\text{typical}} \cdot e^{\eta}$$

where Cl is the value for an individual, $\text{Cl}_{\text{typical}}$ is the typical value for the population, and η is a normally distributed random variable with a mean zero. Both the basic model and the interindividual variability can also be wholly or partially modeled as functions of physiologic covariates, the aim being to reduce the residual degree of interindividual variability.

The basic parameters of the models used here were volume of the central compartment (V_1), volume of the peripheral compartments (V_2 and V_3), clearance (Cl, elimination clearance equal to $V_1 \cdot k_{10}$) and distribution clearances (Q_1 equal to $V_1 \cdot k_{12}$ and Q_2 , equal to $V_1 \cdot k_{13}$). Volume of distribution at steady state (V_{ss}) was equal to V_1 plus V_2 plus V_3 . Models were fitted using NONMEM's first-order conditional estimates with the "centered" option. A model building approach was used, and improvements in three criteria were used to determine if additional

Table 2. Study Population

Patient	Gender	Age (yr)	Weight (kg)	Propofol Infusion Duration	Diagnosis Infusion Rate ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$)	Mean Propofol
1	Male	0.75	7.8	20 h, 35 min	Cardiac surgery	4.0
2	Female	0.58	4.0	15 h	Nonsurgical	6.0
3	Female	1.58	6.0	9 h	Nonsurgical	4.0
4	Female	0.06	3.1	25 h, 30 min	Nonsurgical	3.3
5	Male	1.92	12	28 h, 3 min	Nonsurgical	5.0
6	Female	0.35	3.6	25 h, 30 min	Cardiac surgery	4.7
7	Female	4.33	14	5 h	Cardiac surgery	4.0
8	Male	1.33	9.5	5 h, 10 min	Cardiac surgery	4.0
9	Male	4.17	11.7	10 h	Cardiac surgery	4.0
10	Female	0.60	5.5	16 h, 10 min	Cardiac surgery	4.0
11	Male	0.02	3.8	23 h, 45 min	Cardiac surgery	3.1
12	Male	12.25	33	18 h, 30 min	Cardiac surgery	4.0
13	Female	0.68	6.5	12 h	Cardiac surgery	4.0
14	Male	1.42	10.4	9 h, 45 min	Cardiac surgery	4.0
15	Male	4.08	15.1	6 h, 5 min	Cardiac surgery	4.0
16	Male	0.50	6.5	11 h, 10 min	Cardiac surgery	4.0
17	Female	0.09	3.3	16 h, 5 min	Cardiac surgery	4.0
18	Male	2.25	12.5	5 h, 18 min	Cardiac surgery	4.0
19	Male	1.33	8.9	17 h, 22 min	Cardiac surgery	4.0
20	Male	3.33	13.6	4 h	Cardiac surgery	4.0
21	Female	3.25	11.4	4 h, 50 min	Cardiac surgery	4.0

parameters should be incorporated into the model. These criteria were goodness of fit ($-2 \log$ likelihood) evaluated against a chi-square distribution, determinable precision for all parameters, and visual acceptability.

We first tested models with two and three compartments. When these indicated that three compartments were justified, we subsequently used only three-compartment models. The population pharmacokinetic model was developed by adding interindividual variation parameters until no further model variation could be justified. Next, guided by visual plots, we evaluated models that permitted structural parameters (*i.e.*, clearances and volumes) to differ with covariates. We systematically attempted to model each structural pharmacokinetic parameter as a simple or complex function of age or weight and as a function of gender or type of operation. The justification for each additional effect added to the model was for it to improve the goodness-of-fit statistic ($-2 \log$ likelihood) by more than 3.7 (evaluated against the chi-square distribution, this is equivalent to significance at the 0.05 level) and to result in a visual improvement in the goodness of fit. When all justified additional effects had been added to the model, the necessity for each was tested by removing it from the model and evaluating the resultant fit.

Simulations

To investigate our pharmacokinetic findings, simulations were performed using our optimal model. Concurrently, we performed simulations using the propofol pharmacokinetic model developed by Schuttler and Ihmsen,¹⁸ to allow comparison of our model with a model developed from older healthy children and adults. To

demonstrate the influence of weight in both models, and age in the Schuttler model, profiles were simulated for children of different weights and ages. The assignment of age to weight was based on our study population. We simulated 12-h infusions (our median propofol infusion duration) at a constant rate of $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

Results

Twenty-one children were recruited to the study. Median age was 16 months (range, 1 week to 12 yr), and median weight was 8.9 kg (range, 3.1–33 kg). Details of the patient population and propofol delivery are shown in table 2. Duration of propofol infusion ranged from 4.5 to 28 h (median, 12 h). In three patients, propofol infusion was extended beyond 24 h because planned extubation was delayed and it was considered inappropriate to change to another sedative agent.

Sedation scoring was performed in 20 children (1 child required paralysis, and sedation scores were not performed). Fifteen of these 20 completed the study with $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ morphine, while 5 children (2 post-operative cardiac and 3 noncardiac) required dose increases. At $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol, target sedation scores were achieved in 17 of 20 children. Two of the 17 required a reduction in the infusion rate of propofol because of hypotension. No child had arrhythmias during the infusion. No neonate required more than $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ morphine or $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol. Plasma concentrations of triglyceride and LDL and HDL cholesterol were unaffected by 2% propofol. Urea and electrolytes and liver function test results were not significantly different from baseline.

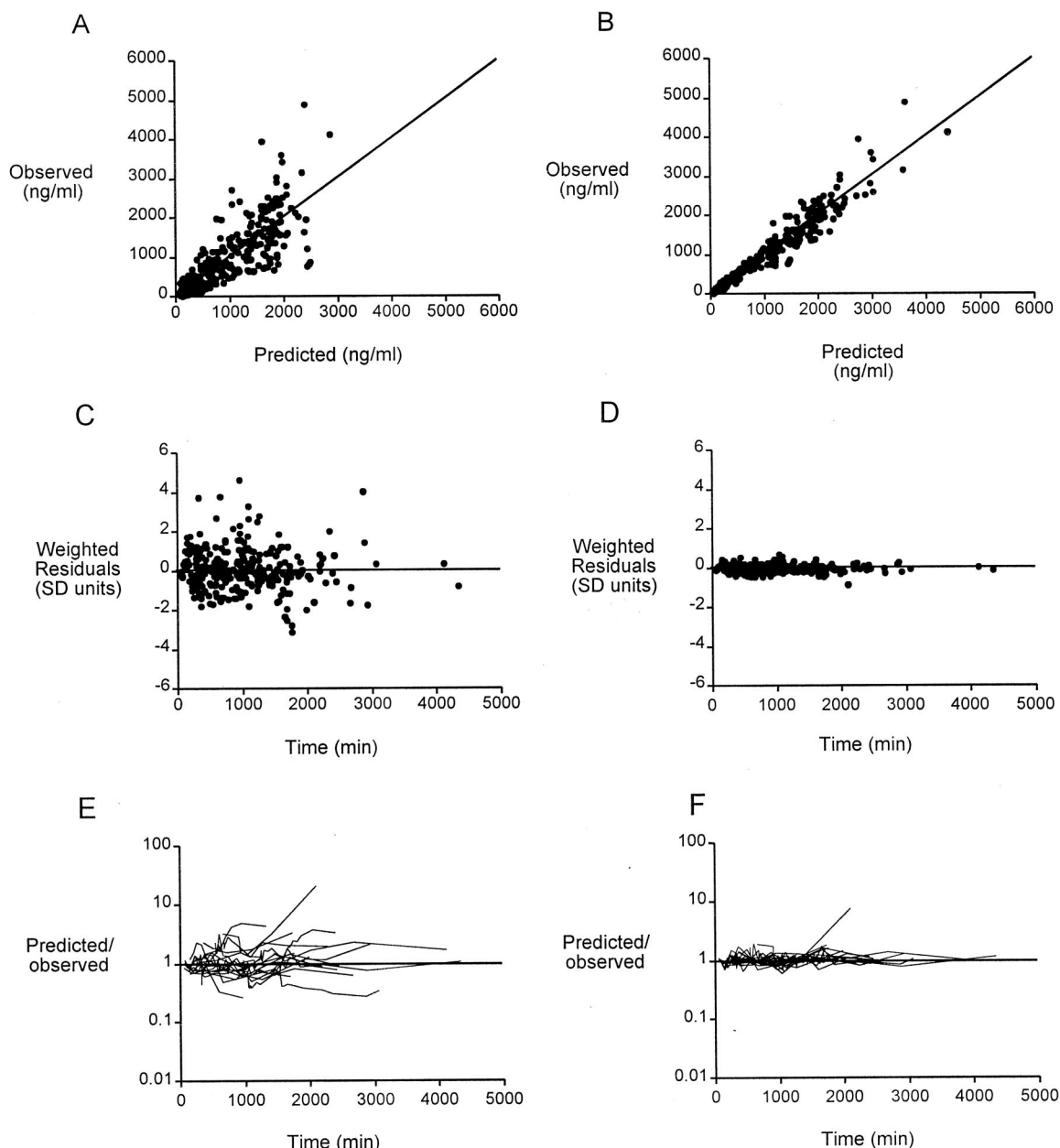


Fig. 1. Plots allowing the evaluation of the optimal model to the data. (A) Observed Cb *versus* population model-predicted Cb. (B) Observed Cb *versus* individualized model-predicted Cb. (C) Weighted residuals *versus* time for the optimal population model. (D) Weighted residuals *versus* time for the optimal individualized models. (E) Population model-predicted/observed Cb for each of the 21 subjects. (F) Individualized model predicted/observed Cb for each of the 21 subjects. Cb = Concentration of propofol in whole blood. The plots of the predicted *versus* observed concentrations (population model [A] and individualized models [B]) demonstrate the overall goodness of fit. A plot of the weighted residuals (or SD units) *versus* time (population model [C] and individualized models [D]) will show whether the pattern of the residuals is dependent on time. Plots of the population model-predicted Cb (E) or individualized model-predicted Cb (F) *versus* observed Cb for each subject will demonstrate if any individual data set is an outlier.

Pharmacokinetics

A three-compartment model with interindividual variation modeled in clearance, slow and fast distributional clearances, and V_1 was accepted. This model had a median prediction error of -1.5% and a median absolute prediction error of 29.7% . Some visual representations of the fit are in figure 1. An abbreviated summary of the model-building process is given in table 3. The optimal model (*i.e.*, the one that fit the data best and in which no

parameter could be removed without significantly worsening the fit) was one with three rather than two compartments. The structural parameters of the model (along with 95% confidence intervals for the "typical values" and the associated degree of interindividual variability) are shown in table 4. The structural parameters Cl , Q_2 , Q_3 , V_1 , and V_2 were all proportional to weight, while the largest of the three compartments (V_3) was related to weight in a complex way with a constant

Table 3. Abbreviated Summary of the Model Building Process

Model Number	Issue Tested	Number of Structural Parameters	Objective Function
1	Two-compartment model (all parameters constant)	4	3,601.462
2	Two-compartment model (all parameters weight related)	4	3,439.831
3	Three-compartment model (all parameters constant) included for completeness only	6	3,608.586
4	Three-compartment model (all parameters weight related)	6	3,366.057
5	V ₃ constant plus weight related	7	3,336.836
6	Model 4 plus clearance differs with type of surgery	7	3,359.891
7	Model 5 plus clearance differs with type of surgery	8	3,333.101

Only those models which improved the fit over a previous model are listed.

* To justify adding a single parameter at the $P = 0.05$ level the objective function should decrease by 3.64. The equivalent value for two parameters (*i.e.*, a single compartment) is 6.

component in addition to the weight-related component. In addition, children recovering from cardiac surgery had significantly reduced propofol clearance. Concentration-*versus*-time profiles for a typical prediction and the most extreme underprediction and overprediction, respectively, are shown in figure 2.

Many combinations of covariate interactions were examined during the course of the model-building process, in particular weight, age, gender, type of operation, and duration of propofol infusion. Age, gender, and duration of propofol infusion were not supported as covariates. The intercompartmental rate constants were calculated from the typical clearance and volume values for cardiac surgery patients. The intercompartmental rate constants were used to construct the context sensitive half-time profiles (time required for a 50% decrement in the blood propofol concentration as a function of infusion duration) for children of different weights, using the computer software package RECOV (fig. 3). RECOV was developed by Steven L. Shafer, MD (Department of Anesthesia, Stanford University, Palo Alto, CA), and is freely available (<http://anesthesia.stanford.edu/pkpd/>).

Simulations

The concentration-*versus*-time profiles for children of different weights (and ages) simulated using our final

pharmacokinetic model and the pharmacokinetic model developed by Schuttler and Ihmsen¹⁸ are shown in figure 4. Compared with our data, the Schuttler model significantly underpredicts the propofol blood concentration resulting from a 12-h infusion at $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, administered to critically ill children after cardiac surgery.

Complications

One child developed persistent hypotension and metabolic acidosis after 5 h of propofol infusion at a constant infusion rate of $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. This child had a mitral valve atresia and total anomalous pulmonary venous drainage and had undergone a Fontan procedure. Metabolic acidosis was apparent at the start of the propofol infusion and persisted after propofol was discontinued. It was a clinical decision to discontinue the propofol, and it was considered that the acidosis was related primarily to poor cardiac output. Midazolam was used as a replacement infusion. The hypotension and acidosis responded over the following 8 h to intravenous fluid and vasoconstrictors. There were no arrhythmias, and the child did not develop bradycardia. The blood steady state concentrations of propofol in this patient were similar to those of the other patients in the study, and the elimination curve was unremarkable. Triglyceride concentrations were normal. The lowest blood pres-

Table 4. Magnitude of Parameters for the Optimal Model

Parameter	Typical Value	95% CI	CV (%)
Clearance ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	30.2	22.5 to 37.9	38
Q_2 ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	16.0	13.6 to 18.4	96
Q_3 ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	13.3	12.2 to 14.4	44
V_1 (l/kg)	0.584	0.465 to 0.703	94
V_2 (l/kg)	1.36	0.99 to 1.73	NA
V_3 (l/kg)	5.67	-0.25 to 11.59*	NA
plus V_3 (l)	103	54.6 to 151.4	—
Cardiac surgery on CI	-25.7%	-41% to 8%*	NA

* These confidence intervals are symmetric approximations. The true 95% C.I. does not include zero.

CI = confidence interval, calculated as parameter estimate $\pm 1.96 \times$ standard error of the estimate; CV = coefficient of variation, determined, where possible, as the typical magnitude of the ETA variables associated with that PK parameter; Clearance = irreversible systemic clearance from the central compartment; Q_2 = distribution clearance for the rapidly equilibrating peripheral compartment; Q_3 = distribution clearance for the slowly equilibrating peripheral compartment; V_1 = volume of the central compartment; V_2 = volume of the rapid peripheral compartment; V_3 = volume of the slow peripheral compartment; NA = not applicable.

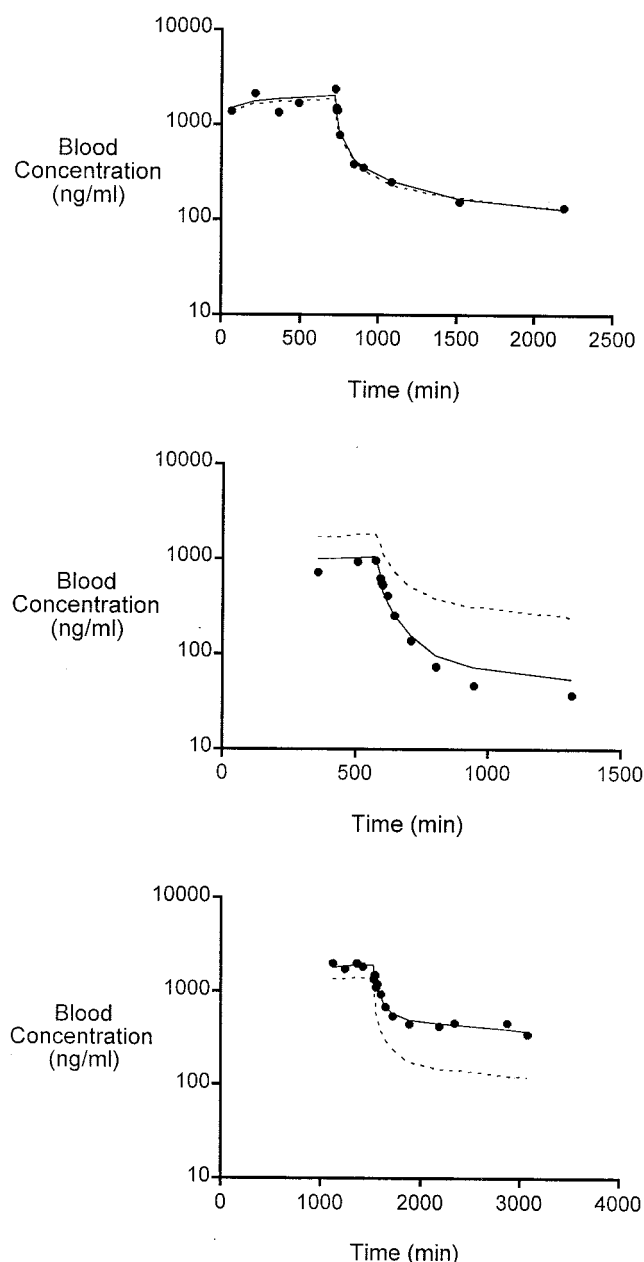


Fig. 2. Examples of model fits to three individuals' propofol concentration data. The dashed line represents the prediction of the "typical value" model. The solid line is the individualized model. (Top) Typical fit. (Middle) The most extreme overprediction. (Bottom) The most extreme underprediction.

sure recorded for this child was 70/45 mmHg, and pulse rate ranged from 150 to 165 beats/min. No other patients developed an acidosis. No other major complications were observed using propofol in this series.

Discussion

Our model demonstrates that critically ill children and infants have a pharmacokinetic profile for propofol that is broadly similar to previously reported studies in well

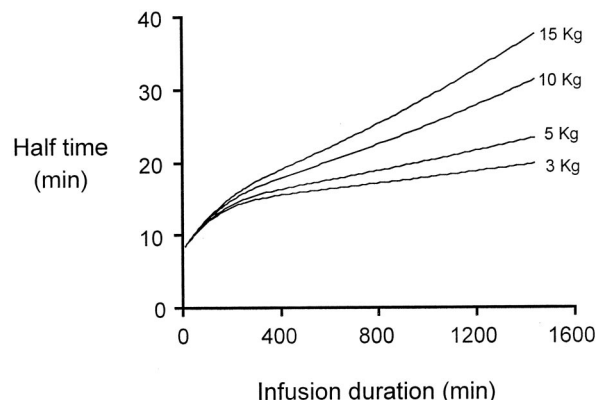


Fig. 3. Context-sensitive half-time for post-cardiac surgery children of different weights.

adults and children^{9-11,19-22} and in critically ill children.¹² However, we found altered kinetics in very small babies and in children recovering from cardiac surgery.

In neonates, our model indicated proportionately increased distribution of propofol into slowly equilibrating tissues compared with older children. This is evidenced by the large constant component of V_3 . This will have more significance in smaller children as the volume of the deep compartment becomes proportionally larger as body weight decreases. The redistribution rate constant from this compartment, k_{31} , is also highly weight dependent with smaller children having a slower rate of drug movement out of V_3 than larger children. In neonates and infants, the combination of a large slow peripheral compartment and slow redistribution rate has relevant effects late after the discontinuation of the infusion in that residual concentrations of propofol are detectable for longer. However, the clinically relevant early context sensitive decrease in blood propofol concentration (context sensitive half-time) is shorter in smaller children after prolonged infusion. The proportionally larger deep compartment allows drug distribution from the central compartment to occur rapidly even after prolonged infusion. The kinetic model therefore indicates that when a propofol infusion is stopped in a young infant, the initial decrease in blood concentration is more rapid, while the later decline is slower than in an older child. This fits with our clinical impression that neonates can emerge from sedation infusions rapidly, but full recovery can be considerably delayed.

Our typical parameter estimates, with the exception of V_3 and K_{31} , are within the ranges reported by Reed and colleagues.¹² Reed *et al.* reported a median V_3/V_1 ratio of 20 and a median V_3/V_2 ratio of 11 for children aged 0.02 to 3.2 yr (personal communication, Michael D. Reed, Pharm.D., Professor of Pediatrics, School of Medicine, Case Western Reserve University, Cleveland, OH, March 2002). This is similar to our parameter estimations in larger children. In 10-kg and 15-kg children (corresponding to children aged 1-4 yr in our study), our V_3/V_1

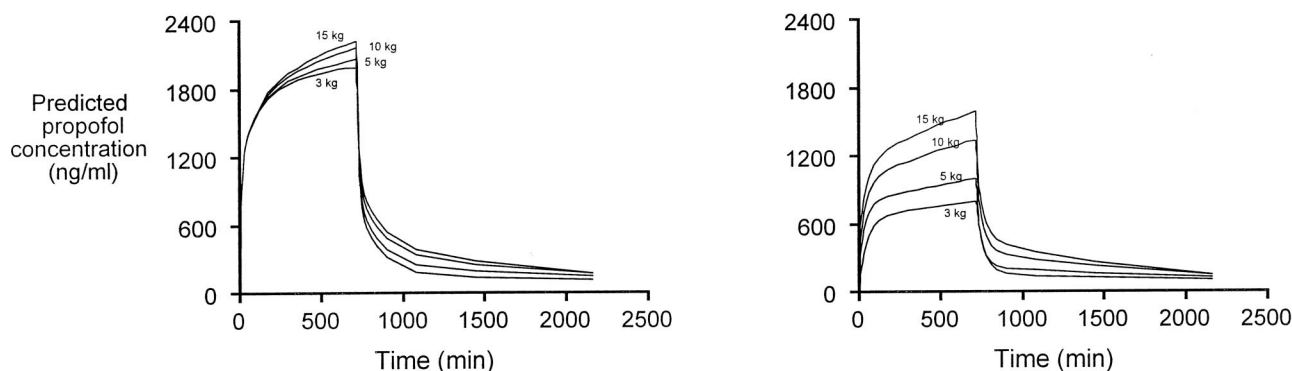


Fig. 4. Pharmacokinetic simulations. (Left) Simulated concentration-versus-time profiles resulting from 12-h propofol infusions ($4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) administered to children of different weights undergoing cardiac surgery using the pharmacokinetic parameters determined in this study. (Right) Simulated concentration-versus-time profiles resulting from 12-h propofol infusions ($4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) administered to children of different weights and ages, using the pharmacokinetic parameter estimates reported by Schuttler and Ihmsen.¹⁸

ratios are 27 and 21, respectively, while our V_3/V_2 ratios are 12 and 9. However, the relative increase in peripheral distribution in smaller babies is demonstrated by our volume ratios for a 3-kg baby, where V_3/V_1 is approximately 68 and V_2/V_1 is 29. The major difference between our study protocol and that performed by Reed and colleagues¹² is that our patients received concomitant morphine infusions, while those of Reed *et al.* received ketorolac. The interactions between propofol and the synthetic opioids are well documented,²³ and it has been reported that alfentanil reduces propofol elimination clearance and increases the deep volume of distribution.²⁴ The interaction between propofol and morphine is less clear, but it is possible that the administration of morphine may have influenced the pharmacokinetics of propofol in our study and may have contributed to our increased apparent volume of distribution. We did not quantify morphine blood concentrations, and morphine administration was not evaluated as a model covariate.

The increased peripheral drug distribution in the smaller babies may be explained by their altered body composition. Total body water, extracellular fluid, and blood volume are considerably larger in neonates and young infants than in older children, when expressed as a percentage of total body weight. Also, reduced plasma protein binding caused by the state of critical illness can have the effect of increasing the apparent distribution volume because more free drug is available for tissue binding.²⁵ In previous pharmacokinetic studies in children, propofol has been administered as a single bolus^{10,11,19} or as a short infusion.^{9,12} The duration of propofol infusion in this study (up to 28 h) was significantly longer, and this will have aided our ability to fully characterize late propofol pharmacokinetics.

As with other studies of propofol pharmacokinetics in children,^{12,19} age was not found to be a significant covariate for our model. The association of weight but not age as a covariate in the model was interesting. The infants and children recruited for the study were not

from a normal population. Specifically, some of the infants who underwent cardiac surgery were below the 10th centile for weight compared with age. Hence, there was little correlation of age with weight. The pharmacokinetic analysis of propofol in children by Kataria and colleagues⁹ found age to be a statistically significant covariate on V_2 but was not thought to be clinically relevant as the actual improvement to the model was very small.

The propofol pharmacokinetic model developed by Schuttler and Ihmsen¹⁸ was based on data from healthy children and adults aged 2–88 yr. Age and weight were included as model covariates. Our simulations of propofol infusions administered to children of different weights and ages describe the differences between our pharmacokinetic parameter values (clearance based on cardiac surgery patients) and those derived by the analysis of Schuttler and Ihmsen (fig. 4). The parameter estimates of Schuttler and Ihmsen demonstrate increased metabolic and distributional clearance, particularly in the smaller babies. This results in an underprediction of the propofol blood concentration compared with the simulations produced using our model. Our simulated age-weight relations were based on the very underweight children seen in our study, and it is therefore not surprising that these simulations demonstrate significant kinetic differences between the two models.

Elimination of morphine is prolonged in children after cardiac surgery.²⁶ This is in keeping with our findings of propofol pharmacokinetics on the pediatric intensive care unit. Our optimal pharmacokinetic model also indicates that patients undergoing cardiac surgery had reduced values for metabolic clearance. Mild liver impairment is common following cardiopulmonary bypass in children and may continue into the postoperative period.²⁷ This could effect the hepatic clearance of propofol. Cardiac surgery patients also demonstrate reduced cardiac output, which may affect propofol elimination. As postcardiac surgery patients provided the majority of our

data, this may potentially limit the applicability of our kinetic parameters to noncardiac surgery, critically ill pediatric patients. However, despite the low number of nonsurgical patients in our study, we were able to detect a statistically significant effect of surgery on clearance.

Concerns about propofol infusion syndrome in children have limited the use of this drug in intensive care, and it is now contraindicated in both the United States and United Kingdom for sedation of children younger than 16 yr. Our study in this patient group demonstrates that the pharmacokinetics, although different, did not result in excessively high blood concentrations of propofol. Current data seem to indicate that the cause of propofol infusion syndrome is an inhibition of mitochondrial function leading to an increase in short and medium chain fatty acids.^{6,8,28} This study was completed within the guidelines recommended at the time for propofol infusion in children, and we saw no indications of propofol infusion syndrome in this series. Our data set included a neonate following a "switch" procedure for transposition of the great arteries, a Blalock Taussig shunt, a repair of Fallots tetralogy, and a Fontan procedure. The results from this study showed that it was feasible to use short-term propofol infusions for the critically ill child and neonate. However, because of the results of a recent clinical trial (unpublished)⁵ that demonstrated significantly higher mortality in children sedated with propofol compared with other sedative agents, propofol has now been withdrawn from use as a sedative agent in critically ill children aged 16 yr or younger. Whether it still should continue to be used as an anesthetic infusion in children who require a brief period of additional anesthesia in the critical care unit after surgery remains debatable.

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