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


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 In 2 patients the dose was reduced because of hypotension, and 1 patient was withdrawn from the study because of an increasing metabolic acidosis.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, 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 0.564 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 phenomena.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 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...
Table 1. Sedation Score for Ventilated Non-Paralyzed Children

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expression</td>
<td>No movement, asleep</td>
<td>Alert, relaxed expression</td>
<td>Anxious, frown, crumpled face, silent cry</td>
</tr>
<tr>
<td>Body movement</td>
<td>No movement, asleep</td>
<td>Some movement, relaxed position</td>
<td>Jerky, uncoordinated, arching</td>
</tr>
<tr>
<td>Agitation</td>
<td>No movement, asleep</td>
<td>Some agitation, can be comforted</td>
<td>Cannot be comforted</td>
</tr>
<tr>
<td>Ventilation</td>
<td>No respiratory effort</td>
<td>Triggering, synchronizing</td>
<td>Asynchrony</td>
</tr>
</tbody>
</table>

Introduction 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 μg·kg⁻¹·h⁻¹. Sedation was maintained with 4 mg·kg⁻¹·h⁻¹ propofol and 20 μg·kg⁻¹·h⁻¹ morphine if sedation scores remained within the target range. Undersedation was treated with dopamine infused at 5 mg·kg⁻¹·h⁻¹ and 20 μg·kg⁻¹·h⁻¹ morphine if sedation scores were not achieved with 40 μg·kg⁻¹·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 5–10 μg·kg⁻¹·min⁻¹ with epinephrine as a second agent. Hypotension associated with low central venous pressure was treated with volume replacement, initially 20 ml/kg crystalloid. If hypotension was considered to result from oversedation, the rate of propofol infusion was reduced in increments of 1 mg·kg⁻¹·h⁻¹ to a minimum of 2 mg·kg⁻¹·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 procedure and analyzed by high-performance liquid chromatography. 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. 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:

\[ \text{Cl} = \text{Cl}_{\text{typical}} e^\eta \]

where Cl is the value for an individual, Cl_{typical} is the typical value for the population, and \( \eta \) 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 (V₁), volume of the peripheral compartments (V₂ and V₃), clearance (Cl, elimination clearance equal to V₁ · k₁₀) and distribution clearances (Q₁ equal to V₁ · k₁₂ and Q₂, equal to V₁ · k₁₃). Volume of distribution at steady state (Vₕᵢ₀) was equal to V₁ plus V₂ plus V₃. 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...
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 compart-
ments. When these indicated that three compartments
were justified, we subsequently used only three-com-
partment 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 mod-
els that permitted structural parameters (i.e., clearances
and volumes) to differ with covariates. We systematically
attempted to model each structural pharmacokinetic pa-
rameter 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 signifi-
cance at the 0.05 level) and to result in a visual improve-
ment 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, simula-
tions were performed using our optimal model. Concur-
rently, we performed simulations using the propofol
pharmacokinetic model developed by Schuttler and Ihm-
sen,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 mg · kg⁻¹ · h⁻¹.

Results

Twenty-one children were recruited to the study. Me-
dian 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 inappro-
priate to change to another sedative agent.

Sedation scoring was performed in 20 children (1 child
required paralysis, and sedation scores were not per-
formed). Fifteen of these 20 completed the study with
20 μg · kg⁻¹ · h⁻¹ morphine, while 5 children (2 post-
operative cardiac and 3 noncardiac) required dose in-
creases. At 4 mg · kg⁻¹ · 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 μg · kg⁻¹ · h⁻¹ morphine or 4 mg · kg⁻¹ · 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.

Table 2. Study Population

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Propofol Infusion Duration</th>
<th>Diagnosis Infusion Rate (mg · kg⁻¹ · h⁻¹)</th>
<th>Mean Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>0.75</td>
<td>7.8</td>
<td>20 h, 35 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>0.58</td>
<td>4.0</td>
<td>15 h</td>
<td>Nonsurgical</td>
<td>6.0</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>1.38</td>
<td>6.0</td>
<td>9 h</td>
<td>Nonsurgical</td>
<td>4.0</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>0.06</td>
<td>3.1</td>
<td>25 h, 30 min</td>
<td>Nonsurgical</td>
<td>3.3</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>1.92</td>
<td>12</td>
<td>28 h, 3 min</td>
<td>Nonsurgical</td>
<td>5.0</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>0.35</td>
<td>3.6</td>
<td>25 h, 30 min</td>
<td>Cardiac surgery</td>
<td>4.7</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>4.33</td>
<td>14</td>
<td>5 h</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>1.33</td>
<td>9.5</td>
<td>5 h, 10 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>4.17</td>
<td>11.7</td>
<td>10 h</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>0.60</td>
<td>5.5</td>
<td>16 h, 10 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>0.02</td>
<td>3.8</td>
<td>23 h, 45 min</td>
<td>Cardiac surgery</td>
<td>3.1</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>12.25</td>
<td>33</td>
<td>18 h, 30 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>0.68</td>
<td>6.5</td>
<td>12 h</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>1.42</td>
<td>10.4</td>
<td>9 h, 45 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>4.08</td>
<td>15.1</td>
<td>6 h, 5 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>16</td>
<td>Male</td>
<td>0.50</td>
<td>6.5</td>
<td>11 h, 10 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>17</td>
<td>Female</td>
<td>0.09</td>
<td>3.3</td>
<td>16 h, 5 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>18</td>
<td>Male</td>
<td>2.25</td>
<td>12.5</td>
<td>5 h, 18 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>19</td>
<td>Male</td>
<td>1.33</td>
<td>8.9</td>
<td>17 h, 22 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>20</td>
<td>Male</td>
<td>3.33</td>
<td>13.6</td>
<td>4 h</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
<tr>
<td>21</td>
<td>Female</td>
<td>3.25</td>
<td>11.4</td>
<td>4 h, 50 min</td>
<td>Cardiac surgery</td>
<td>4.0</td>
</tr>
</tbody>
</table>
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
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 the 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 Ihmsen 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 mg · kg⁻¹ · 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 mg · kg⁻¹ · 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 persisting 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-

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**Table 3. Abbreviated Summary of the Model Building Process**

<table>
<thead>
<tr>
<th>Model Number</th>
<th>Issue Tested</th>
<th>Number of Structural Parameters</th>
<th>Objective Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Two-compartment model (all parameters constant)</td>
<td>4</td>
<td>3,601.462</td>
</tr>
<tr>
<td>2</td>
<td>Two-compartment model (all parameters weight related)</td>
<td>4</td>
<td>3,439.831</td>
</tr>
<tr>
<td>3</td>
<td>Three-compartment model (all parameters constant) included for completeness only</td>
<td>6</td>
<td>3,608.586</td>
</tr>
<tr>
<td>4</td>
<td>Three-compartment model (all parameters weight related)</td>
<td>6</td>
<td>3,366.057</td>
</tr>
<tr>
<td>5</td>
<td>V₃ constant plus weight related</td>
<td>7</td>
<td>3,336.836</td>
</tr>
<tr>
<td>6</td>
<td>Model 4 plus clearance differs with type of surgery</td>
<td>7</td>
<td>3,359.891</td>
</tr>
<tr>
<td>7</td>
<td>Model 5 plus clearance differs with type of surgery</td>
<td>8</td>
<td>3,333.101</td>
</tr>
</tbody>
</table>

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.

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**Table 4. Magnitude of Parameters for the Optimal Model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>95% CI</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (ml · kg⁻¹ · min⁻¹)</td>
<td>30.2</td>
<td>22.5 to 37.9</td>
<td>38</td>
</tr>
<tr>
<td>Q₂ (ml · kg⁻¹ · min⁻¹)</td>
<td>16.0</td>
<td>13.6 to 18.4</td>
<td>96</td>
</tr>
<tr>
<td>Q₃ (ml · kg⁻¹ · min⁻¹)</td>
<td>13.3</td>
<td>12.2 to 14.4</td>
<td>44</td>
</tr>
<tr>
<td>V₁ (l/kg)</td>
<td>0.584</td>
<td>0.465 to 0.703</td>
<td>94</td>
</tr>
<tr>
<td>V₂ (l/kg)</td>
<td>1.36</td>
<td>0.99 to 1.73</td>
<td>NA</td>
</tr>
<tr>
<td>V₃ (l/kg)</td>
<td>5.67</td>
<td>-0.25 to 11.59*</td>
<td>NA</td>
</tr>
<tr>
<td>plus V₃ (l)</td>
<td>103</td>
<td>54.6 to 151.4</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiac surgery on CI</td>
<td>-25.7%</td>
<td>-41% to 8%*</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

CI = confidence interval, calculated as parameter estimate ± 1.96 × 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; Q₁ = distribution clearance for the rapidly equilibrating peripheral compartment; Q₂ = distribution clearance for the slowly equilibrating peripheral compartment; V₁ = volume of the central compartment; V₂ = volume of the rapid peripheral compartment; V₃ = volume of the slow peripheral compartment; NA = not applicable.

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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 adults and children and in critically ill children. 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. 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 \( V_3/V_1 \)
morphine may have in is less clear, but it is possible that the administration of clearance and increases the deep volume of distribution. The interaction between propofol and morphine reported that alfentanil reduces propofol elimination 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 colleagues 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, and it has been reported that alfentanil reduces propofol elimination clearance and increases the deep volume of distribution. 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. In previous pharmacokinetic studies in children, propofol has been administered as a single bolus or as a short infusion. 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, 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 colleagues 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 Ihmsen 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. 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. 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

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Fig. 4. Pharmacokinetic simulations. (Left) Simulated concentration-versus-time profiles resulting from 12-h propofol infusions (4 mg · kg⁻¹ · 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 mg · kg⁻¹ · h⁻¹) administered to children of different weights and ages, using the pharmacokinetic parameter estimates reported by Schuttler and Ihmsen.

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data, this may potentially limit of 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. 

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) 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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