Pharmacokinetics of a Single Bolus of Propofol in Chinese Children of Different Ages

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Background: There is no information about the pharmacokinetic profile of propofol in Chinese children younger than 3 yr. This study was designed to determine a complete pharmacokinetic profile of a single dose of propofol in Chinese children of different ages.

Methods: Arterial blood samples were obtained from 35 children with an American Society of Anesthesiologist physical status of I or II at 2, 4, 6, 8, 10, 20, 30, 45, 60, 90, 120, and 180 min after a single bolus intravenous injection of propofol (3 mg/kg). The plasma concentrations of propofol were measured using high-performance liquid chromatography with an ultraviolet detector. A population model was used to estimate the pharmacokinetics of propofol.

Results: A three-compartment pharmacokinetic model best described the pharmacokinetics of propofol. Clearance was 0.185 l/min; the volume of distribution of the central compartment was 7.41 l, the peripheral volumes of distribution were 54.6 and 7.2 l, and the intercompartmental clearances were 0.614 and 0.692 l/min for a child of the average weight of 13.7 kg. The half-lives were 2.67, 14.89, and 310.60 min. Covariate models were applied, and weight was found to be significant covariate for the clearance and volume of distribution parameters. No significant age effect could be demonstrated on clearance or volume of distribution parameters after weight was taken into account.

Conclusions: This study supports the case that the pharmacokinetic properties of propofol do not differ substantially across Chinese children of different ages after weight has been accounted for.

Although the use of propofol for induction and maintenance of anesthesia has gained great popularity among pediatric anesthetists, there is only limited scientific evidence about its use in children younger than 3 yr. Therefore, propofol is not licensed for use in children younger than 3 yr in many countries.1 Murat et al.2 attempted a complete pharmacokinetic profile of propofol after a single dose in white healthy children aged 1–3 yr. However, without direct comparison of this age group of children with the children older than 3 yr, they concluded that this age group of children had a larger central compartment volume together with a higher clearance of propofol than all values reported in older children. Furthermore, it is known that race affects pharmacokinetics of certain anesthetic drugs.3 Therefore, there is a lack of pharmacokinetics of propofol in Chinese children younger than 3 yr, although older Chinese children have been studied.4

Therefore, the specific aim of this study was to determine a complete pharmacokinetic profile of a single dose of propofol in different-aged Chinese children ranging from 4 months old to 9 yr old to provide further scientific evidence regarding the use of propofol for induction in children younger than 3 yr old.

Materials and Methods

Study Design

Having obtained the approval from the Local Research Ethics Committee and written informed parental consent from the 2nd Affiliated Hospital of Wenzhou Medical College, Wenzhou, China, we recruited 35 pediatric patients (American Society of Anesthesiologists physical status of I or II) undergoing general or urinary surgery for congenital megacolon, urinary tract defects, or bilateral undescended testis (from February to September 2002 at the 2nd Affiliated Hospital of Wenzhou Medical College). Patients with cardiopulmonary disease, renal and hepatic dysfunction, or central nervous system disease were excluded from the study.

All children were premedicated with 2.0–4.0 mg/kg ketamine and 0.02–0.03 mg/kg atropine intramuscularly 1 h before surgery. In the operating room, a pulse oximetry finger probe was attached to the patient. An indwelling cannula was then inserted into a large vein in the forearm for induction of general anesthesia, and a second indwelling cannula was inserted into a contralateral radial artery for the continuous measurement of arterial blood pressure and for the collection of blood samples. Other standard monitoring included electrocardiogram, arterial blood pressure, heart rate, and end-tidal carbon dioxide concentration. Midazolam, 0.1–0.2 mg/kg, was given intravenously before induction. Anesthesia was induced with 3.0–5.0 μg/kg fentanyl, 3.0 mg/kg propofol (1% Diprivan; AstraZeneca, Lyton, United Kingdom) within 20 s, and 0.1 mg/kg vecuronium, and additional boluses of muscle relaxant were given according to clinical judgment. Time 0 was taken at the completion of the propofol injection. After the intubation, anesthesia...
was maintained with 1.0–1.3 minimum alveolar concentration of isoflurane in a carrier gas of 50% nitrous oxide in oxygen. Ventilation was adjusted to maintain end-tidal carbon dioxide concentration between 4.0–4.5%.

Acquisition, Sample Handling, and Processing
Propofol was administered via an indwelling intravenous cannula (22 or 24 gauge) in the forearm. Arterial blood samples of 0.5 ml were taken at 2, 4, 6, 8, 10, 20, 30, 45, 60, 90, 120, and 180 min after propofol injection for measurement of propofol concentrations. All samples were collected in heparinized tubes and centrifuged (4,000 rpm, 10 min) within 30 min of collection. The supernatant was collected into polypropylene tubes and stored at −4°C until subsequent analysis. Propofol concentrations in plasma were measured within 14 weeks by high-performance liquid chromatography (HP1100; Hewlett-Packard, Houston, TX) using the method described by Wang et al.5 with coefficients of variation of 5.5%.

Pharmacokinetic Analysis
Population parameter values were estimated using a nonlinear mixed effects model (NONMEM) for both between-subject and residual variability (random effects), and differences between parameters were related to available covariates (fixed effects).

Structural Model. One-, two-, and three-compartment pharmacokinetic models were fitted to the data using subroutines from the NONMEM library (ADVAN1 TRANS2, ADVAN3 TRANS4, and ADVAN11 TRANS4, respectively).6 The parameters of central (V1) and peripheral (V2 and V3) compartment volumes, total body clearance (CL), intercompartmental clearance between central and peripheral 1 (Q2), and intercompartmental clearance between central and peripheral 2 (Q3) were estimated for the three-compartment pharmacokinetic model.

Models for Weight and Age Changes in the Pharmacokinetics of Propofol. Previous publications have shown the merit of including models for weight and age to explain changes in pharmacokinetics of several drugs in children.7,8 Furthermore, publications regarding propofol also support this in both adults and children.9,10 An allometric weight model11–15 was applied to standardize the pharmacokinetic parameters using a standard weight (WTSTD) of 13.7 kg (mean weight of patients in the study). An empirical model was tested to describe changes with age for clearance parameters but was found to offer no significant improvement in prediction after weight had already been applied.

Clearance Model.

$$CL_i = CL_{GRP} e^{PPVCL_i},$$

where

$$CL_{GRP} = CL \cdot F_{WT},$$

and where

$$F_{WTG} = \left(\frac{WT}{WT_{STD}}\right)^{3/4}.$$  

CLGRP is the covariate predicted group value for clearance, and CLi is the individual clearance for the ith patient.

Volume Model.

$$V_i = V_{GRP} e^{PPV},$$

where

$$V_{GRP} = V \cdot F_{WT},$$

and where

$$F_{WTV} = \frac{WT}{WT_{STD}}.$$  

VGRP is the covariate predicted group value for volume, and Vi is the individual volume for the ith patient.

Error Model. The between-subject variability in model parameters was modeled by a proportional variance model. Residual, unidentified variability was described in the final model using a proportional error model. This error model assumes that the residual vari-

<table>
<thead>
<tr>
<th>Model Building</th>
<th>Description</th>
<th>Objective Function Value</th>
<th>No. of Structural Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base 1 comp</td>
<td>No covariates</td>
<td>−229,632</td>
<td>2</td>
</tr>
<tr>
<td>Base 2 comp</td>
<td>No covariates</td>
<td>−1,091,991</td>
<td>4</td>
</tr>
<tr>
<td>Base 3 comp</td>
<td>No covariates</td>
<td>−1,269,007</td>
<td>6</td>
</tr>
<tr>
<td>3-comp weight*</td>
<td>Weight on clearance and volume</td>
<td>−1,355,567</td>
<td>6</td>
</tr>
<tr>
<td>3-comp weight age</td>
<td>Weight on clearance and volume; age on clearance</td>
<td>−1,359,073</td>
<td>8</td>
</tr>
<tr>
<td>3-comp group</td>
<td>Weight on clearance and volume; age on clearance; effect of group</td>
<td>−1,362,216</td>
<td>12</td>
</tr>
</tbody>
</table>

* Final model.
Comp = compartment.
ability is proportional to the size of the measurements.

\[ Y = F \cdot e^{ERR(1)} \]

where \( F \) is the predicted propofol concentration (without residual error), and \( Y \) is the individual prediction including a proportional (ERR(1)) residual error component. ERR(1) was assumed to be normally distributed random variable with mean 0. A combined proportional and additive error model was originally applied, but the additive error was found to be minimal.

**Computation.** Model building was performed using NONMEM version V release 1.1 (NONMEM Project Group, University of California, San Francisco, CA) under MS-DOS (Microsoft Windows) on a Pentium 4 3-GHz personal computer using Microsoft Windows XP and the g77 FORTRAN compiler (Free Software Foundation, Inc., Boston, MA). All model building was performed using the first-order conditional estimation method with the interaction estimation option.

**Decision Criteria.** Only models that successfully minimized were considered for further use. A decrease of 3.84 points in the objective function value for each additional parameter was required before the more complex model was considered, unless the more complex model had less bias shown by visual inspection of the diagnostic and concentration time plots.

**Simulation.** Simulation of a 1-h operation based on the propofol regimen described in the British National Formulary was performed using the final population pharmacokinetic model in NONMEM. The simulation was based on a 1% injection and an initial infusion of 3 mg/kg over 30 s. The maintenance infusion was at 12 mg·kg\(^{-1}\)·h\(^{-1}\). The average weight for each of the groups A, B, and C was used, and 1,000 replicates were run.

### Table 3. Final Parameter Estimates for Standard Individual of 13.7 kg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (95%CI)</th>
<th>BSV* (SE [CV]†)</th>
</tr>
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<tbody>
<tr>
<td>CL, l/min</td>
<td>0.185 (0.137–0.233)</td>
<td>0.658 (0.131)</td>
</tr>
<tr>
<td>V1, l</td>
<td>7.41 (5.62–8.3)</td>
<td>0.333 (0.060)</td>
</tr>
<tr>
<td>Q1, l/min</td>
<td>0.614 (0.54–0.688)</td>
<td>0.348 (0.061)</td>
</tr>
<tr>
<td>V2, l</td>
<td>54.6 (46.6–62.6)</td>
<td>0.142 (0.073)</td>
</tr>
<tr>
<td>Q2, l/min</td>
<td>0.692 (0.558–0.826)</td>
<td>0.491 (0.097)</td>
</tr>
<tr>
<td>V3, l</td>
<td>7.2 (5.328–9.072)</td>
<td>0.451 (0.130)</td>
</tr>
</tbody>
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**Proportional error** 0.084 (0.123)§

| T1/2, 1, min | 2.67 |
| T1/2, 2, min | 14.89 |
| T1/2, 3, min | 310.6 |

* Between-subject variability (BSV) expressed as an approximate coefficient of variation (CV). † SE expressed as a CV of the BSV term. ‡ SE expressed as a CV of the proportional error term.

Table 4. General Model for Propofol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>General Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL =</td>
<td>0.185* (weight/13.7)(^{0.75})</td>
</tr>
<tr>
<td>V1 =</td>
<td>7.41* (weight/13.7)</td>
</tr>
<tr>
<td>Q1 =</td>
<td>0.614* (weight/13.7)(^{0.75})</td>
</tr>
<tr>
<td>V2 =</td>
<td>54.6* (weight/13.7)</td>
</tr>
<tr>
<td>Q2 =</td>
<td>0.692* (weight/13.7)(^{0.75})</td>
</tr>
<tr>
<td>V3 =</td>
<td>7.2* (weight/13.7)</td>
</tr>
</tbody>
</table>

CL = clearance; Q1 and Q2 = intercompartmental clearances; V1 = volume of distribution of the central compartment; V2 and V3 = peripheral volumes of distribution.

### Results

All 35 children completed the study. The demographic data are summarized in Table 1.

Table 2 describes the model building process undertaken to arrive at the final model for propofol pharmacokinetics in this study. A three-compartment pharmacokinetic model using weight as a covariate on clearance and volume parameters best described the pharmacokinetics of propofol in the study population. Table 3 shows the parameter estimates of the final pharmacokinetic model which included an allometric weight model, which was applied to standardize the pharmacokinetic parameters using a standard weight of 13.7 kg. Clearance (CL) was 0.185 l/min, volume of distribution of the central compartment (V1) was 7.41 l, the peripheral volumes of distribution were 54.6 l (V2) and 7.2 l (V3), and the intercompartmental clearances were 0.614 l/min (Q1) and 0.692 l/min (Q2) for a child of the average weight of 13.7 kg. The half-lives were 2.67, 14.89, and 310.6 min. The context-sensitive half-life was 28 min calculated by interpolation. Table 3 also shows the between-subject variability on the structural parameters of the model. Table 4 shows the general model for propofol. Table 5 shows the expected parameter values for patients who weighed 9.7, 13.6, and 18.5 kg, respectively. These weights represent the mean weight of each of the age groups A, B, and C.

### Table 5. Expected Parameter Values for Patients Who Weighed 9.7, 13.6, and 18.5 kg

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Weight, kg</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>9.7</td>
</tr>
<tr>
<td>B</td>
<td>13.6</td>
</tr>
<tr>
<td>C</td>
<td>18.5</td>
</tr>
</tbody>
</table>

CL = clearance; Q1 and Q2 = intercompartmental clearances; V1 = volume of distribution of the central compartment; V2 and V3 = peripheral volumes of distribution.

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Figure 1 shows the mean of the raw data split into the age groups with the corresponding SD bars. Figure 2 shows the measured data with the population predicted fit from the final model with covariates and the corresponding 90% prediction interval. Goodness-of-fit plots of the final model for the complete study are shown in figures 3–5.

When covariate models were applied, weight was found to be a significant covariate for the clearance and volume of distribution parameters, as shown in table 2 and figure 6. No significant age effect could be demonstrated on clearance or volume of distribution parameters after weight had been taken into account, as demonstrated by the marginal decrease in objective function value (table 2).

Figure 7 shows a simulation of the predicted pharmacokinetic time course of a 1-h operation based on the population model obtained from these children. The pharmacokinetic profiles are similar among the three age groups.

Discussion

Based on the pharmacokinetic analysis of propofol after single bolus administration to Chinese children, no age difference in the pharmacokinetic parameters was found after weight was accounted for. It has been reported that both age and race can alter the pharmacokinetic profile of propofol. Clinical observational studies have demonstrated that children require larger doses of propofol for both induction and maintenance of anesthesia than adults do. The British National Formulary recommends that for induction of anesthesia, children older than 8 yr usually need a higher dose per kilogram of propofol than adults do. The greater central volume of distribution (V) and total body clearance (CL) in children, particularly in younger ones, have been attributed to the increased requirement in children.

Within the population of children, however, there seems to be an increased propofol dose requirement for induction, maintenance, or both and a slow recovery from anesthesia in infants and young children. With the immature renal function and altered hepatic enzyme activity and drug absorption, pharmacokinetics in infants and children younger than 3 yr are more variable compared with older children. The confirmation of the pharmacokinetic profile of propofol for this age group, therefore, would be relevant to pediatric anesthesia. In addition, information about this aspect of
the drug might enable propofol to be made available in many countries that currently do not hold licenses for its use. Furthermore, a commercial pediatric propofol target-controlled infusion system for children younger than 3 yr is not yet available in pediatric anesthesia, although STANPUMP software\textsuperscript{††} based on a pediatric pharmacokinetic model for children aged between 3 and 10 yr\textsuperscript{25} has been developed. Information on the pharmacokinetic profile of a single dose of propofol in the full age range of children is fundamental to improvement of pediatric propofol target-controlled infusion systems.

To date, there are few studies\textsuperscript{2,26} designed to determine the pharmacokinetics of propofol in white children younger than 3 yr as a single group, rather than mixing with older children or adults.\textsuperscript{9,10,19,24,27,28} Without direct comparison among different ages, Murat \textit{et al.}\textsuperscript{2} could only conclude that both \( V \) and \( CL \) were greater on a per-kilogram basis than values reported in older children and adults. There has been no information available on the pharmacokinetics of propofol in Chinese children younger than 3 yr old. A pharmacokinetic profile after a single dose of propofol in a full range of ages in children is rarely reported. All reported studies\textsuperscript{4,20–22} investigated Chinese children older than 3 yr of age.

In this study, we found consistency of pharmacokinetic parameters across the population age and no evidence of an effect of age on those parameters, either examining age in three strata or with age as a covariate term in analysis of the study population after weight was accounted for. This consistency of pharmacokinetic parameters across the age group from 4 months to 9 yr further supports the statement of the British National Formulary\textsuperscript{14}: For induction of anesthesia, children younger than 8 yr may need higher doses (2.5–4 mg/kg) than children older than 8 yr (usually 2.5 mg/kg). Having used the final population pharmacokinetic model to simulate 1-h surgery based on the propofol regimen in the

\textbf{Fig. 6.} Individual predicted clearance for the final model \textit{versus} weight. The \textit{solid} (regression) \textit{line} is the covariate model for the dependence of clearance on weight determined in the final model, and the \textit{broken line} represents the 95\% prediction interval. The prediction interval is the clearance range for a given weight based on the between subject variability.

\textbf{Fig. 7.} Simulation of the propofol infusion regimen as stated in the British National Formulary with the assumption of 30 s taken for induction of anesthesia. \textit{Top panel} based on the mean weight of the children in group A of the study, 9.7 kg. \textit{Center panel} based on the mean weight of the children in group B of the study, 13.6 kg. \textit{Bottom panel} based on the mean weight of the children in group C of the study, 18.5 kg. The \textit{solid line} represents the population prediction, and the \textit{dotted line} represents the 90\% prediction interval.
British National Formulary, we found that the pharmacokinetic profiles are similar among the three age groups. This may suggest that in pediatric patients, dosing recommendations to achieve and maintain therapeutic concentrations for induction or in a pediatric target-controlled infusion system could be simplified as regimens for older or younger than 8 yr. Our findings may also provide evidence to facilitate the process of licenses in countries that currently do not hold licenses for its use.

There are limitations in the current study. First, the children were premedicated with ketamine and then anesthetized using various other medications, e.g., midazolam, fentanyl, and isoflurane. Pharmacokinetics of propofol can be markedly influenced by drug interactions.29 However, drug interactions should not affect consistency of pharmacokinetics of propofol across the population age when the children were treated with standardized anesthetic techniques. Second, it would have been more appropriate to include neonates, infants younger than 1 yr, and children aged 1–3 yr as homogeneous when attempting to characterize propofol pharmacokinetic behavior. Furthermore, there were only two female subjects in the study, thus eliminating the ability to draw conclusions about the effect of sex on the pharmacokinetics.

In conclusion, the plasma concentrations of propofol decreased rapidly in all three age groups after a single dose injection. The pharmacokinetics of propofol in all three groups of Chinese children were best described by a three-compartment pharmacokinetic model. Weight alone accounted for the difference in pharmacokinetic parameters between the different age groups.

References

17. Westrin P: The induction dose of propofol in infants 1–6 months of age and in children 10–16 years of age. ANESTHESIOLOGY 1991; 74:455–8
29. Eilers H, Niemann C: Clinically important drug interactions with intravenous anaesthetics in older patients. Drugs Aging 2003; 20:969–80