Pharmacokinetics of Propofol after a Single Dose in Children Aged 1–3 Years with Minor Burns

Comparison of Three Data Analysis Approaches

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Background: No complete pharmacokinetic profile of propofol is yet available in children younger than 3 yr, whereas clinical studies have demonstrated that both induction and maintenance doses of propofol are increased with respect to body weight in this age group compared to older children and adults. This study was therefore undertaken to determine the pharmacokinetics of propofol after administration of a single dose in aged children 1–3 yr requiring anesthesia for dressing change.

Methods: This study was performed in 12 children admitted to the burn unit and in whom burn surface area was less than or equal to 12% of total body surface area. Exclusion criteria were: unstable hemodynamic condition, inappropriate fluid loading, associated pulmonary injury, or burn injury older than 2 days. Propofol ($4 \, mg \cdot kg^{-1}$) plus fentanyl ($2.5 \, \mu g \cdot kg^{-1}$) was administered while the children were bathed and the burn area cleaned during which the children breathed spontaneously a mixture of oxygen and nitrous oxide (50:50). Venous blood samples of 300 µl were obtained at 5, 15, 30, 60, 90, and 120 min, and 3, 4, 8, and 12 h after injection; an earlier sample was obtained from 8 of 12 children. The blood concentration curves obtained for individual children were analyzed by three different methods: noncompartmental analysis, mixed-effects population model, and standard two-stage analysis.

Results: Using noncompartmental analysis, total clearance of propofol (± SD) was $0.053 \pm 0.013 \, l \cdot kg^{-1} \cdot min^{-1}$, volume of distribution at steady state $9.5 \pm 3.7 \, l \cdot kg^{-1}$, and mean residence time 188 ± 85 min. Propofol pharmacokinetics were best described by a weight-proportional three-compartmental model in both population and two-stage analysis. Estimated and derived pharmacokinetic parameters were similar using these two pharmacokinetic approaches. Results of population *versus* two-stage analysis are as follow: systemic clearance 0.049 *versus* $0.048 \, l \cdot kg^{-1} \cdot min^{-1}$, volume of central compartment 1.03 *versus* $0.95 \, l \cdot kg^{-1}$, volume of distribution at steady state 8.09 *versus* $8.17 \, l \cdot kg^{-1}$.

Conclusions: The volume of the central compartment and the systemic clearance were both greater than all values reported in older children and adults. This is consistent with the increased propofol requirements for both induction and maintenance of anesthesia in children aged 1–3 yr. (Key words: Anesthesia: pediatric. Pharmacokinetics: propofol.)

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THE use of propofol for induction and/or maintenance of anesthesia has gained wide acceptance among pediatric anesthesiologists since the availability of the EMLA cream allowing for pain-free venopuncture.[1,2] Clinical studies have demonstrated that infants and young children require larger doses of propofol for both induction and maintenance of anesthesia than older children and adults.[3–7] This has been attributed to an increased volume of the central distribution compartment together with a large clearance of the drug.[8–12] These age-related pharmacokinetic differences may explain why adult pharmacokinetic models fail to predict the blood concentrations actually measured in children aged 1–12 yr.[13] In this age group, the pharmacokinetics of most drugs like opioids or thiopental exhibit wide differences as compared to

adults or older children. Only one pharmacokinetic study of propofol in infants and children younger than 3 yr is available.[14] In this study, propofol clearance is high, similar to that measured in children 3–12 yr, but unfortunately, other pharmacokinetic parameters are not fully reliable owing to the short sampling time.

Our study was therefore undertaken to determine the pharmacokinetics of propofol after a single injection in children 1–3 yr age admitted to the burn unit for burn injury involving up to 12% of body surface area. The choice of patients was guided by local ethical committee considerations. It was assumed that children with minor burns are not physiologically different from fit children in the same age group.

Materials and Methods

Study Design

The study was approved by the ethics committee (CCPPRB, Hotel-Dieu, Paris) and written informed parental consent was obtained before the start of the study. Children aged 1–3 yr, ASA physical status 1, with a burn surface area less than or equal to 12% of body surface area and requiring general anesthesia for dressing change were included in the study. Exclusion criteria were: unstable hemodynamic condition defined as systolic arterial pressure less than 70 mmHg + 2 × age in years, urine output < 0.5 ml·kg^{-1}·h^{-1} and/or urine specific gravity > 1.025 or <1.005 and/or total protein < 45 g·l^{-1}, burn surface area $> 12\%$ of body surface area, burn injury older than 2 days, and inhalation injury requiring mechanical ventilation.

Twelve children entered the study. All received 0.2 mg·kg^{-1} midazolam and 10 μg·kg^{-1} atropine intravenously 10 min before bathing procedure. Anesthesia was induced with 4 mg·kg^{-1} propofol in 20 s (manual infusion). Analgesia was provided if necessary with an initial bolus of fentanyl (2–3 μg·kg^{-1}) and additional bolus according to clinical judgment. All children were breathing spontaneously a mixture of 50% oxygen and 50% nitrous oxide through a face mask throughout the procedure. Pulse oximetry was monitored. Rectal temperature was measured before and after the procedure.

Measurement of Propofol Concentrations in Whole Blood

Venous blood samples of 300–500 μl were taken from an intravenous catheter in a vein in the opposite arm or leg before propofol injection and then at 5, 10,

15, 30, 60, 90, 120, 180, and 240 min, and 8 and 12 h after injection. After the first four patients were studied, it was deemed appropriate to obtain an additional earlier blood sample at 1 min for the remaining patients. After thorough mixing with ammonium oxalate, venous blood samples were stored at 4°C until subsequent analysis. Whole blood concentrations of propofol were measured within 3 weeks after sampling by high-pressure liquid chromatography using the method described by Plummer[15] with coefficients of variation of 2.4% and 12.8% for 2000 ng·ml^{-1} and 25 ng·ml^{-1}, respectively. The limit of quantification was 10 ng·ml^{-1}.

Data Analysis

Three different approaches were used to estimate the pharmacokinetic parameters: noncompartmental analysis, mixed-effects population model, and standard two-stage analysis.

Noncompartmental Analysis

Moment analysis is a noncompartmental method assuming that the times taken for individual drug molecules to pass through the body may be treated as a continuous density function that encompasses any number of first-order processes. Clearance (Cl), mean residence time, and apparent volume of distribution at steady state (V$_{ss}$) were calculated nonparametrically using standard moment analysis.[16] The area under the concentration versus time curve was calculated for each patient using linear trapezoids when concentrations were increasing, and log-linear trapezoids when concentrations were decreasing. The terminal slope was estimated using log-linear regression of the terminal portion of each curve. The clearance was calculated as

$$CL = \frac{Dose}{AUC}$$

The first moment curve (concentration × time vs. time) was calculated for each set of data and the area under the first moment curve also was calculated using an interpolation-integration method. The mean residence time of propofol was calculated as

$$MRT = \frac{AUMC}{AUC}$$

The apparent V$_{ss}$ was calculated as
V$_{ss}$ = CL × mean residence time
The population parameter estimates were calculated as the average of the individual values.

528

Mixed-effects Population Analysis

A full description of data analysis was recently published by Kataria *et al.*[9] Method will therefore be described briefly. The population pharmacokinetic parameters were determined using the mixed-effects nonlinear regression program NONMEM, version IV level 1.1.[17] NONMEM estimated the typical value of each volume and clearance parameter for two- and three-compartment models in the population. For the two-compartment model, NONMEM estimated V_1, the volume of the central compartment, V_2, the volume of the peripheral compartment, Cl_1, the irreversible systemic clearance of drug from the central compartment, and Cl_2, the distribution clearance to the peripheral volume. For the three-compartment model, NONMEM estimated V_1 and Cl_1, defined as for the two-compartment model, V_2 and Cl_2, the volume and distribution clearance for the rapidly equilibrating compartment, and V_3 and Cl_3, the volume and distribution clearance for the slowly equilibrating compartment. Interindividual variability (expressed as percent coefficient of variation) was determined for these estimated parameters.

The NONMEM analysis included incorporation of patient covariates in the model. The specific covariates investigated were weight, age, and total proteins. The covariates were incorporated into the model as a scalar times covariates (*e.g.,* clearance was proportional to weight). We independently tested the volumes of distribution as a linear function of the weight with clearances independent of the weight, the clearance term as a linear function of the weight with the distribution volume independent of the weight, as well as a "weight-scaled" model in which all volumes and clearances were assumed to be a linear function of weight. The optimal model was determined by minimizing the value of the NONMEM objective function. From the volumes and clearances estimated by NONMEM, we calculated the hybrid rate constants and fractional coefficients using standard pharmacokinetic equations.[18,19]

Standard Two-stage Approach

The blood concentration curves obtained for individual children were fitted to the sum of exponential functions derived from Colburn[20] and interpreted by two-stage analysis as two- and three-compartment open mamillary models. Pharmacokinetic modeling was performed using the SIPHAR program (version 4.0)[21] for fitting the curves, with a weighing function $1/y^2$

using calculated values. The quality of the fit of the three exponential models was assessed by the presence of a random scatter of the data around a calculated value, and by visual assessment of the residuals of the observed values from the fitted curves. Weight, age, and total protein were investigated as covariates as in the previous analysis.

Results

Twelve children completed the study: 11 boys and 1 girl. Mean ($\pm$ SD) weight was 11.9 ± 2.6 kg (range 8.7–18.9 kg), and mean age was 17.8 ± 6.2 months (range 12–31 months). Mean rectal temperatures before, immediately after, and 60 min after bath were respectively, $37.4 \pm 0.8°C$, $36.9 \pm 0.8°C$, and $37.4 \pm 0.8°C$. Mean total protein values were $58.6 \pm 5.7 \text{ g} \cdot l^{-1}$ (range 48–70 $\text{g} \cdot l^{-1}$). The loss of eyelash reflex was obtained 21.6 ± 9.5 s after propofol injection. The dose of propofol administered was 3.95 ± 0.1 $\text{mg} \cdot \text{kg}^{-1}$ (range 3.5–4.2), mean dose of fentanyl was 3.2 ± 2.1 $\mu g \cdot kg^{-1}$. Recovery defined by Stewart score equal to 6^{22} was obtained 9.0 ± 4.9 min after nitrous oxide was discontinued.

All data points were used for pharmacokinetic modeling. Individual propofol concentration curves *versus* time are shown in figure 1. The first venous sample was obtained at 1 min in 6 of the 12 children, at 2 min and 3 min in 2 others, respectively, and was not done in the remaining 4 patients. Exact sampling time was taken into account for calculations.

Noncompartmental Analysis

Total clearance ($\pm$ SD) of propofol was $0.053 \pm 0.013 \text{ l} \cdot kg^{-1} \cdot min^{-1}$, V_{ss} $9.5 \pm 3.7 \text{ l} \cdot kg^{-1}$, and mean residence time 188 ± 85 min.
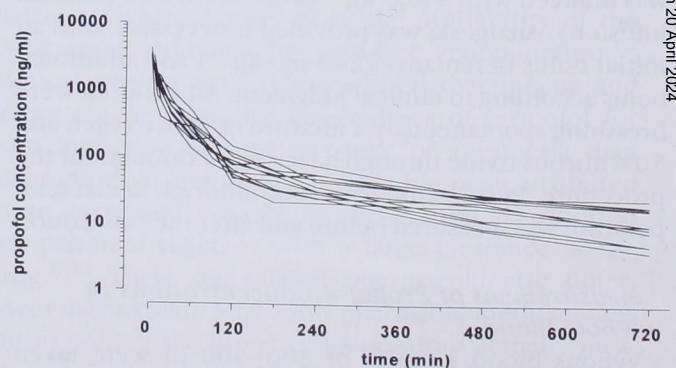
Fig. 1. Individual propofol blood concentrations *versus* time curves.

Mixed-effects Population Analysis

Pharmacokinetics were better described by a three-compartment open mamillary model than by a two-compartment model, as assessed by the objective function results (1253 *vs.* 1318). In the three-compartment model, the use of weight as covariate for both clearance and volume improved the description of the data (objective function 1230 *vs.* 1253), whereas the use of weight applied solely to either volume or clearance was not better than no covariates. Age and total protein were also tested as covariates, but data objective function was greater than that of the weight as covariate. The quality of the fit for the weight-proportional pharmacokinetic model, expressed as measured/predicted blood concentrations, is shown on figure 2. Variability of V_1 was estimated by NONMEM as close to zero (0.01%).

Two-stage Analysis

The evolution of blood concentrations over time also could be best described by a three-compartment open mamillary model in all patients. The weight-proportional model also produced better estimates than no covariates. No relationship was found between age and V_{ss}, V_1, or Cl with linear regression analysis.

The values of estimated and derived parameters measured with population and two-stage analysis are presented in table 1. The results obtained with these two methods were pretty similar. Propofol was distributed rapidly from a large central compartment. The total apparent V_{ss} was greater than total body volume indicating extensive redistribution. Total body clearance was very high.

Discussion

The pharmacokinetics of propofol in children aged 1–3 yr were best described by a weight-proportional three-compartment model as in most adult and pediatric studies.[8–11,23–25]

Three different approaches were used to analyze the data. The results of the three methods are in close agreement. Because extensive sampling was used for each patient, only 8% of the area under the concentration *versus* time curve were extrapolated to estimate V_{ss} in the noncompartmental model, whereas 92% were measured. The results of the mixed-effect population model and of two-stage analysis were similar, in agreement with data previously reported by Kataria *et al.*[9]
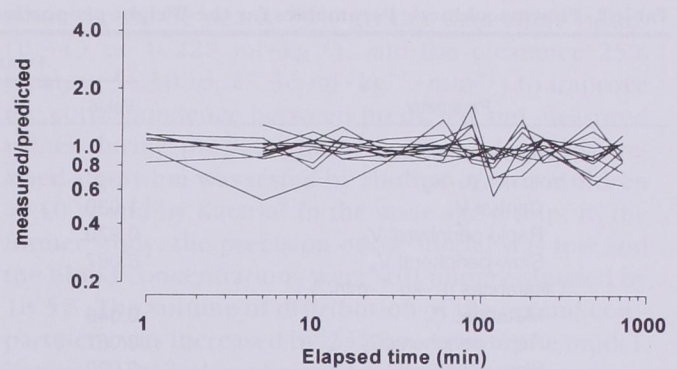

Fig. 2. Measured/predicted values for all 12 children for the weight-proportional mixed-effects population model (NON-MEM).

Regardless of the modeling approach, the pharmacokinetics of propofol of children aged 1–3 yr of age differ from those reported in older children and adults. Young children have a larger volume of the central compartment and a higher clearance compared to older children and adults, as shown in table 2. Total body clearance of propofol is highly dependent on hepatic blood flow, because its hepatic extraction is close to 1.0. This explains why clearance values of propofol are roughly similar in children older than 3 yr and adults. The clearance measured in the current study is 20–55% higher than that measured in pediatric studies performed in children older than 3 yr. This may be explained by the relative increase in liver blood flow in this age group, because the liver accounts for 4–5% of body weight in infants and young children and only 2% in adults. Our values are also greater than those measured in a recently published study of six children aged 1–3 yr (38.7 $ml \cdot kg^{-1} \cdot min^{-1}$, ranging from 28.5 to 45.7 $ml \cdot kg^{-1} \cdot min^{-1}$).[14] No drug known to decrease hepatic blood flow was used in our study, whereas most pediatric pharmacokinetic studies have been performed during anesthesia with halogenated agents. The two anesthetic drugs used in our study (midazolam and fentanyl) are known to have no effect on propofol pharmacokinetics in adults.[26–28]

The volume of the central compartment is 30–80% higher than the values reported in children aged 3 yr or older[8–11] and at least twice the mean values published in adults.[29] Consequently, the younger the child, the lower the plasma concentration obtained after administering a given single dose on a per-weight basis. These data account for the finding that the induction dose of propofol increases as the age of the child de-

MURAT *ET AL.*

Table 1. Pharmacokinetic Parameters for the Weight-proportional Models

Parameter	Population		Two-stage	
	Value	% CV	Value	% CV
Estimated parameters				
Volumes ($L \cdot kg^{-1}$)				
Central V_1	1.030	0.01	0.95	23.2
Rapid peripheral V_2	0.970	38.1	1.262	
Slow peripheral V_3	6.087	34.5	6.967	
Clearances ($L \cdot kg^{-1} \cdot min^{-1}$)				
Metabolic C_1	0.049	19.1	0.048	26.1
Rapid peripheral C_2	0.067	56.7	0.081	
Slow peripheral C_3	0.020	31.9	0.021	
Derived parameters				
Volumes ($L \cdot kg^{-1}$)				
Steady state	8.09		8.17	
Fractional coefficients				
A ($\mu g \cdot L^{-1}$)	0.711		0.771	
B ($\mu g \cdot L^{-1}$)	0.273		0.215	
C ($\mu g \cdot L^{-1}$)	0.017		0.013	
Exponents (min^{-1})				
α	0.1769		0.2005	
β	0.0273		0.0246	
γ	0.0023		0.0021	
Half-lives (min)				
α	5.12		4.11	
β	26.1		25.4	
γ	365.2		319.9	
Microrate constants (min^{-1})				
K10	0.048		0.053	
K12	0.064		0.085	
K13	0.020		0.022	
K21	0.071		0.064	
K31	0.003		0.003	

CV = coefficient of variation.

creases.[3-7] The very high volume of the central compartment, however, may be overestimated in this study as well as in most pediatric studies,[9,10] because the first exponential phase intercept may be underestimated as a consequence of less extensive sampling in children during the first 10 min after administration. However,

Table 2. Mean Estimated Pharmacokinetic Parameters in This Study and Other Pediatric Studies and One Adult Study

	Current Study (population *vs.* two-stage)		Raoof[14]	Saint-Maurice[10]	Valtonen[11]	Jones[8]	Kataria[9]	Adults[25,*]
Population	1–3 yr		11–43 mo	4–7 yr	3–10 yr	4–12 yr	3–11 yr	45 yr
Site of sampling and	vein		vein	vein	vein	vein	vein	vein
time (min)	720		240	1440	1440	1440	NA	600
VD_{ss} ($L \cdot kg^{-1}$)	8.09	8.17	2.4	10.9	2.16	5.01	9.7	2.3
V_1 ($L \cdot kg^{-1}$)	1.03	0.95	—	0.722	0.53	0.6	0.52	0.35
C_1 ($L \cdot kga-1 \cdot min^{-1}$)	0.048	0.049	0.039	0.031	0.032	0.040	0.034	0.030

Vd_{ss} = volume of distribution at steady state; V_1 = volume of the central compartment; C_1 = systemic clearance.

* Two-compartment model (best fit).

no differences were observed among the 6 children in whom the first blood sample was obtained at 1 min and the remaining 6 who had their first sample performed at 2, 3, or 5 min. In addition, the V_1 estimated in all pediatric studies is based on venous samples, which would be expected to produce a larger V_1 than the arterial samples used in most adult studies. This is especially true for propofol, because the arteriovenous concentration difference is as high as 25–30% during stepdown infusion.[30] However, because both sampling times and site of sampling are similar in all pediatric studies, our data support the effect of age on the size of central compartment, an effect that has been previously reported in older children compared to adults.[9]

This study was performed in burn patients within the first 48 h after injury. All children were ASA physical status 1 and the burn surface area was less than or equal to 12% of body surface area. Pharmacokinetics of many drugs are known to be changed in burn patients.[31,32] These changes may be related to impairment of organ perfusion during the initial phase, and afterward to increased blood flow and enzyme induction during the hypermetabolic state. In addition, edema in burned and nonburned areas can result in an apparent increase in the central or total volume of distribution and binding proteins may be decreased, which will in turn modify the kinetics of highly bound drugs. All of these changes have been described in patients with major burn injuries. This does not apply to our population. Indeed, no child in our study had hemodynamic instability, none needed inotropic support, and all had creatinine values within the normal range for their age. Total albumin was measured in 8 of the 12 patients just before propofol administration and was $39.8 \pm 6.1 \text{ g} \cdot \text{l}^{-1}$, and total protein was greater than $45 \text{ g} \cdot \text{l}^{-1}$ in all children. It has been reported that propofol binding to albumin was not changed in cirrhotic patients in whom total albumin was as low as $36 \pm 5 \text{ g} \cdot \text{l}^{-1}$.[33] We therefore believe that our data are relevant for normal healthy children aged 1–3 yr.

The larger central compartment together with the higher clearance explain the increased requirements of propofol for both induction and maintenance of anesthesia in young children compared to older children; the latter also will require more propofol than adults. Age-related pharmacokinetic differences may explain why adult pharmacokinetic model-driven algorithms overpredict systematically the measured blood concentrations in children aged 2–10 yr.[13] Marsh et al.[13] calculated that the volume of central compart-

ment should be nearly 50% greater than adult values ($0.343 \text{ vs. } 0.228 \text{ ml} \cdot \text{kg}^{-1}$), and the clearance 25% greater ($34.30 \text{ vs. } 27.36 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) to improve the correspondence between predicted and measured values during propofol infusion in children. The revised algorithm was tested by Short et al.[34] in children 4–10 yr and by Kataria[9] in the same age group. In the former study, the precision of the model was low and the blood concentrations were still underestimated by 18.5%. The volume of distribution of the central compartment was increased by 25% to improve the model. Kataria et al.[9] also observed that the parameters reported by Marsh et al.[13] consistently predict higher concentrations than observed in their own study.

In summary, children aged 1–3 yr have a larger central compartment volume together with a higher clearance of propofol as compared to older children and adults. Both of them provide a rationale for the increased induction and maintenance doses of propofol in this age group compared to older children and adults.

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