

Propofol Pharmacokinetics and Pharmacodynamics for Depth of Sedation in Nonventilated Infants after Major Craniofacial Surgery

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Background: To support safe and effective use of propofol in nonventilated children after major surgery, a model for propofol pharmacokinetics and pharmacodynamics is described.

Methods: After craniofacial surgery, 22 of the 44 evaluated infants (aged 3–17 months) in the pediatric intensive care unit received propofol ($2\text{--}4\text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) during a median of 12.5 h, based on the COMFORT-Behavior score. COMFORT-Behavior scores and Bispectral Index values were recorded simultaneously. Population pharmacokinetic and pharmacodynamic modeling was performed using NONMEM V (GloboMax LLC, Hanover, MD).

Results: In the two-compartment model, body weight (median, 8.9 kg) was a significant covariate. Typical values were $\text{Cl} = 0.70 \cdot (\text{BW}/8.9)^{0.61} \text{ l/min}$, $V_c = 18.8 \text{ l}$, $Q = 0.35 \text{ l/min}$, and $V_{ss} = 146 \text{ l}$. In infants who received no sedative, depth of sedation was a function of baseline, postanesthesia effect (E_{max} model), and circadian night rhythm. In agitated infants, depth of sedation was best described by baseline, postanesthesia effect, and propofol effect (E_{max} model). The propofol concentration at half maximum effect was 1.76 mg/l (coefficient of variation = 47%) for the COMFORT-Behavior scale and 3.71 mg/l (coefficient of variation = 145%) for the Bispectral Index.

Conclusions: Propofol clearance is two times higher in nonventilated healthy children than reported in the literature for ventilated children and adults. Based on the model, the authors advise a propofol dose of 30 mg/h in a 10-kg infant to achieve values of 12–14 on the COMFORT-Behavior scale and 70–75 on the Bispectral Index during the night. Wide pharmacodynamic variability emphasizes the importance of dose titration.

TO correct craniosynostosis, most infants undergo surgery in the first years of life. Because of edematous eyelids, separation from parents and the need to stay in the intensive care unit for control of vital signs, and the possible development of neurologic sequelae, these children often experience stress postoperatively. Although

propofol is widely used for sedation in the adult intensive care unit, its use is subject to debate in sedated children in the pediatric intensive care unit since the report of five deaths in children receiving high doses ($> 5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) of propofol.¹ In general, larger doses of propofol are required in children, and it is suggested that this is because of differences in pharmacokinetics,² sensitivity,³ or both.

To date, there are no population models in children investigating the pharmacodynamics to study the variability between and within children. As a pharmacodynamic endpoint, a number of clinical sedation scores have been devised for use in children, in which the COMFORT-Behavior (COMFORT-B) scale^{4,5} would be a reliable alternative to the original, most used COMFORT scale.⁶ The Bispectral Index (BIS) may have benefits in comparison with clinical sedation scores because it assesses sedation continuously and may provide an objective, quantitative measure of the level of sedation.⁷ However, to date, the BIS has only been validated in children older than 1 yr.

Our clinical experiences regarding the use of propofol evaluated by the COMFORT-B in young children in the pediatric surgical intensive care unit (PSICU) have recently been published by Prins *et al.*⁸ In the current article, propofol pharmacokinetics and pharmacodynamics characterized by use of the COMFORT-B and BIS on the postoperative sleep pattern in nonventilated infants are described using population modeling, to select appropriate doses in infants and to support the safe and effective use of propofol.

Materials and Methods

The study was performed in the PSICU of the Erasmus Medical Center–Sophia Children's Hospital, Rotterdam, The Netherlands. The study protocol was approved by the ethics committee of the Erasmus Medical Center–Sophia Children's Hospital. Written informed consent was obtained from the parents. The studied infants, the design, the sedative and analgesic regimen, and safety parameters are presented in detail in the article of Prins *et al.*⁸ and are shortly repeated as relevant to this article.

Patients

Eligibility criteria included major craniofacial surgery, age between 1 month and 2 yr, and postoperative ad-

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Table 1. Patient Characteristics of Agitated Infants and Nonagitated Infants

	Agitated		Nonagitated
	Propofol	No Sedative	No Sedative
Sex, M/F	15/7	8/5	5/4
Age, months	10 (3.8–17.3)	10.9 (3.2–18.5)	8.8 (4.0–12.4)
Weight, kg	8.9 (4.8–12.5)	9.3 (5.1–11)	8.3 (5.5–9.6)
Height, cm	71 (60–76)	72 (58–80)	70 (61.5–77)
CYP genotype			
mutant frequencies			
2B6*1/*5	2		
2B6*1/*6	5		
2B6*6/*6	1		
2B6*1/*7	1		
2C9*1/*2	4		
2C9*1/*3	3		
2C19*1/*2	7		
2C19*2/*2	1		
Infusion duration, h	12.5 (6.0–18.1)	—	—

Data are presented as median (minimum–maximum).

mission to the PSICU. The children were randomly allocated to receive propofol or midazolam if sedative medication was judged necessary on the basis of the COMFORT-B score (score ≥ 17). Infants were excluded when they had respiratory infections, epilepsy, hypertriglyceridemia or family histories of hypercholesterolemia, or history of allergy to propofol, eggs, or soybean oil.

Patient characteristics of the group in which no sedation was necessary (nonagitated group) and the group in which sedation was needed (agitated group) are presented in table 1. Infants who received midazolam could be used for pharmacokinetic and pharmacodynamic analysis before midazolam administration if more than two COMFORT-B observations were available for the description of the postoperative sleep pattern in the agitated group. These infants are represented in table 1 as the agitated, no sedative group. All patients had normal hepatic and renal functions.

Anesthesia

Standardized anesthesia was induced with thiopental (5 mg/kg) or sevoflurane and fentanyl (2.5 μ g/kg), and the infants were paralyzed with vecuronium (0.1 mg/kg). Thereafter, the infants underwent intubation and mechanical ventilation. Anesthesia was maintained with isoflurane, oxygen, and air, and fentanyl was given as needed. A median total dose of 17.9 (10.0–32.9) μ g/kg fentanyl was administered during surgery. Approximately 2 h before extubation, a loading dose of acetaminophen (40 mg/kg) was administered rectally. After the operation, the patients were admitted to the PSICU for a minimum of 24 h, depending on the clinical condition.

Sedative and Analgesic Regimen

Pharmacodynamic data collection was started at arrival at the PSICU. The COMFORT-B score, which has been

validated in pediatric intensive care, was used as a pharmacodynamic endpoint.^{4,5} The COMFORT-B scale assesses six behavioral items: alertness, calmness, muscle tone, body movement, facial tension, and crying (non-ventilated children) or respiratory response (ventilated children). All items range from 1 (no distress) to 5 (severe distress), resulting in a total score varying from 6 to 30. The interobserver reliability represented by linearly weighted κ was greater than 0.65 for all nurses and the principal investigator. In addition, the BIS was recorded continuously and noted at 15-min intervals (BIS® A 2000 version 3.12; Aspect Medical Systems, Natick, MA; with pediatric BIS® sensors). The BIS ranges from 100 (awake) to 0 (isoelectric electroencephalogram). Propofol, 6% (Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands^{9,10}), was given by a central venous line into a running saline infusion by a B. Braun Medical infusion pump (Melsungen, Germany) to a summed rate of 3 ml/h. For propofol, the doses were increased or decreased as needed up to a maximum of 4 mg \cdot kg⁻¹ \cdot h⁻¹. When patients were inadequately sedated with 4 mg \cdot kg⁻¹ \cdot h⁻¹ propofol, midazolam was added. One patient received an additional dose of 0.1 mg/kg followed by 0.05 mg/kg midazolam, one patient received two doses of 0.1 mg/kg, and two patients received a single bolus of midazolam. These responses were excluded from the analysis. To determine whether restlessness was induced by pain, the trained nurses also obtained the visual analog scale score. Patients received the standard four daily doses of 120–240 mg acetaminophen rectally.¹¹ In more than 99% of the observations, the visual analog scale score was less than 4.

Blood Sampling

Arterial samples (250 μ l) were taken before the start of the propofol infusion; at approximately 30 or 45, 60 or 90, and 120 min after the start of the propofol infusion; three times in steady state; just before and 1 h after dose adjustment; just before stopping; and 15 or 30, 45 or 60, 120, and 150 min after the end of the infusion.

Analytical Methods

Propofol concentrations were measured in whole blood using high-performance liquid chromatography with fluorescence detection as described in a previous study from our laboratory.^{3,12} Blood samples were collected in oxalate tubes and stored at 4°C until analysis (within 1 week). The limit of quantification was 0.035 mg/l, and the between-day coefficients of variation were less than or equal to 6.0%.

Genomic DNA was isolated from EDTA blood (MasterAmp; Epicenter Technologies, Madison, WI). Cytochrome P450 (CYP) 2B6 mutations 516G>T, 785A>G, and 1459C>T were analyzed (alleles *4, *5, *6, *7, and *9). Polymerase chain reaction–restriction fragment

length polymorphism analyses were performed as described previously¹³ with the exception of using *Bst*NI as restriction enzyme instead of *Sly*I. Analysis for the 1459C>T polymorphism was performed using primers 5'-CTGTTGCAGTGGACATTTG-3' and 5'-ATCTCACTCCTGCACTCAC-3' in a polymerase chain reaction with an initial step of 7 min at 94°C, followed by 30 cycles of (1 min at 94°C, 1 min at 57°C, 1 min at 72°C) and concluded with a final extension step of 6 min at 72°C. The polymerase chain reaction product was digested with *Bgl*II. CYP2C9*2 and *3 and CYP2C19*2 and *3 analyses were performed on the LightCycler® (Roche Diagnostics, Mannheim, Germany), using the CYP2C9 and CYP2C19 kits (Roche Diagnostics), respectively.

Data Analysis

The Non-Linear Mixed Effect Modeling (NONMEM) program (version V; GloboMax LLC, Hanover, MD)¹⁴ was used for population analysis. S-plus (version 6.2; Insightful software, Seattle, WA) was used to visualize the data. NONMEM estimates the mean pharmacokinetic and pharmacodynamic parameters of the population and the interindividual variability and the residual error, minimizing the objective function ($-2 \log$ likelihood). The NONMEM option of the first-order conditional estimation (method 1) with η - ε interaction was used. Model development was performed in four steps: (1) choice of the structural pharmacokinetic or pharmacodynamic model, (2) choice of the residual model, (3) covariate analysis, and (4) internal validation of the model. Discrimination between different models was made by comparison of the objective function. A value of $P < 0.005$, representing a decrease of 7.8 in the objective function, was considered statistically significant. In addition, the diagnostic plots (observed *vs.* individually predicted, observed *vs.* population predicted, time *vs.* weighted residuals, and population predictions *vs.* weighted residuals) for examining bias and precision, the confidence interval of the parameter estimates, the correlation matrix, and visual improvement of the individual plots were used to evaluate the model.

Covariate Analysis

Covariates were plotted independently against the individual *post hoc* parameter estimates and the weighted residuals to identify their influence. Tested covariates were body weight, age, body surface area, body mass index (if height was known), and sex. The pharmacokinetic parameters were also tested for correlation with heart frequency, blood pressure, triglycerides, and the CYP isoforms (2B6*4, *5, *6, *7, *9, 2C9*2, 2C9*3, 2C19*2, 2C19*3). In addition, the influence of the total dose of fentanyl administration during surgery on the pharmacodynamics was assessed.

Potential covariates were separately incorporated, and a significant covariate that most reduces the objective

function was left in the model. Additional covariates had to reduce this objective function further to be retained in the model. The choice of the model was further evaluated as discussed above.

Validation

A bootstrap resampling method was used to assess the stability of the parameter estimates and the robustness of the final model.¹⁵ A bootstrap involves repeated random sampling to produce another data set of the same size but with a different combination of individuals. The mean parameter values and coefficients of variation (CVs) of the bootstrap replicates were compared with the estimates of the original data set.

Pharmacokinetic Model

The parameters of a two-compartment model were fitted to the log-transformed data and parameterized in terms of volume of steady state (V_{ss}), volume of the central compartment (V_c), clearance (Cl), and intercompartmental clearance (Q) using subroutine ADVAN 5. The central volume was related to the volume of distribution at steady state as

$$V_c = V_{ss} / (1 + \theta). \quad (1)$$

The individual value of the parameters of the i th subject was modeled by

$$\theta_i = \theta_{\text{mean}} \cdot e^{\eta_i}, \quad (2)$$

where θ_{mean} is the population mean and η_i is assumed to be a Gaussian random variable with zero mean and variance ω^2 . The residual error was described with a proportional error model. This means for the j th observed log-transformed concentration of the i th individual the relation (Y_{ij}):

$$Y_{ij} = \text{Log}c_{\text{pred},ij} + \varepsilon_{ij}, \quad (3)$$

where c_{pred} is predicted transformed propofol concentration and ε_{ij} is a random variable with mean zero and variance σ^2 .

Simulation

To compare the pharmacokinetic results with previously published pharmacokinetic models, simulations were performed using the model developed by Knibbe *et al.*,³ Rigby-Jones *et al.*,¹⁶ and Schüttler and Ihmsen.¹⁷

Pharmacodynamic Model

Depth of sedation was characterized with postoperative natural sleep pattern (PNSP) and propofol effect (PEF).

$$S_{ij} = \text{PNSP}_{ij} - \text{PEF}_{ij}, \quad (4)$$

where S_{ij} is the j th observed sedation level in the i th subject.

The postoperative natural sleep pattern (PNSP) was

described as a function of three equations allowing the depth of sedation to increase and decrease during the first postoperative night in the absence of a sedative.

$$\text{PNSP}_{ij} = \text{BSL}_i + \text{PAEFF}_{ij} - \text{CNR}_{ij}, \quad (5)$$

in which BSL represents the level of sedation at arrival at the PSICU, PAEFF represents the postanesthesia effect, and CNR represents the circadian night rhythm.

For estimation of the interindividual variability of the baseline, log-normal distributions were assumed. This means for the i th individual:

$$\text{BSL}_i = \text{BSL}_{\text{mean}} \cdot e^{\eta_i}, \quad (6)$$

where BSL_{mean} is the population mean and η_i is a Gaussian random variable with zero mean and variance ω^2 .

Postanesthesia effect (PAEFF) was assumed to wash out in time postoperatively by an E_{max} model, resulting in a decrease of the depth of sedation to a maximum estimated score (S_{max}) for the COMFORT-B and 100 (awake) for the BIS.

$$\text{PAEFF}_{ij} = (\text{PAE}_{\text{max},i} \cdot T_{\text{PS},ij}^{\gamma}) / (T_{50,\text{PS},i} + T_{\text{PS},ij}^{\gamma}), \quad (7)$$

where PAE_{max} is the maximal effect from BSL to the maximal score S_{max} , T_{PS} is the time (minutes) postsurgery, $T_{50,\text{PS}}$ is the time (minutes) postsurgery at half maximum postanesthesia effect, and γ is the steepness of the time-*versus*-response relation. Interindividual variability of $T_{50,\text{PS}}$ and γ were assumed to be log-normally distributed.

Circadian night rhythm (CNR) was modeled by

$$\text{CNR} = A \cdot \sin((\text{TIME} - O) \cdot (2\pi/\text{Fr})), \quad (8)$$

where O denotes the onset of the natural night dip in minutes from 12:00 h. The end of the circadian night dip (wake-up time) was assumed at 7:00 h, because at this time point, the light is turned on, nursing care is optimized, and parents arrive at the PSICU. A (COMFORT-B or BIS units) is the amplitude of the night dip, and $2\pi/\text{Fr}$ (minutes) is the frequency of the oscillations.

Propofol effect (PEF) was related to the pharmacokinetic model-predicted individual propofol concentration (C_{ij}) by a simple E_{max} model:

$$\text{PEF}_{ij} = (E_{\text{max},i} \cdot C_{ij}) / (EC_{50i} + C_{ij}), \quad (9)$$

where $E_{\text{max},i}$ is the maximum possible propofol effect (equal to $S_{\text{max}} - 6$ on the COMFORT-B scale and 100 on the BIS scale) in the i th subject, assuming that the response will reach the maximum effect at doses sufficiently higher than $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol. EC_{50} is the propofol concentration (mg/l) at half maximum effect, in which the interindividual variability was assumed to be log-normally distributed. The residual error in the COMFORT-B score and BIS was best characterized by a proportional and an additive error model, respectively.

$$Y_{ij} = \text{COMFORT} - B_{\text{pred},ij} \cdot (1 + \varepsilon_{1,ij}) \quad (10)$$

$$Y_{ij} = \text{BIS}_{\text{pred},ij} + \varepsilon_{2,ij}, \quad (11)$$

where Y_{ij} represents the observed effect in the i th subject at the j th time point.

Table 2. Parameter Estimates of the Basic Pharmacokinetic Model, the Body Weight Power Model, and the Stability of the Parameters Using the Bootstrap Validation

Parameter	Basic Model, Mean (CV%)	Body Weight Power Model, Mean (CV%)	BS Body Weight Power Model, BS Mean (CV%)
Fixed effects			
Cl, l/min	0.69 (6.9)	$= \text{Cl}_{\text{std}} \cdot (\text{BW}/8.9)^b$	
Cl _{std} , l/min	—		0.70 (5.3)
b	—	0.61 (19.7)	0.59 (33.8)
V _{ss} , l	144 (32.1)	146 (31.2)	148 (32.0)
Q, l/min	0.34 (11.9)	0.35 (11.0)	0.35 (11.1)
V _c , l	20.3 (27.9)	18.8 (30.0)	16.8 (46.0)
ALAG ₁ , min	0	0	—
ALAG ₂ , min	40.20 (3.1)	40.20 (3.0)	38.10 (16.3)
Fraction (ALAG)	0.52 (24.1)	0.52 (24.3)	0.47 (31.1)
Interindividual variability, %			
Cl	27 (44.9)	20 (40.0)	20 (48.3)
V _{ss}	136 (34.6)	145 (38.4)	126 (44.8)
ClV _{ss}	49 (34.0)	49 (29.3)	43 (33.4)
Residual error, %			
ε	37 (21.0)	37 (20.7)	36 (20.4)
Performance measures			
−2LL	−141.5	−155.8	−176.2

−2LL = objective function; ε = residual error proportional calculated as square root of the variance; ALAG = lag time of delivery; b = power scaling parameter; BS = bootstrap validation; Cl = clearance in an individual; Cl_{std} = clearance in a standardized individual of 8.9 kg; CV = coefficient of variation of the parameter values; fraction = fraction of the population with ALAG = 0; interindividual variability = square root of the exponential variance of η minus 1; Q = intercompartmental clearance; V_c = central volume (related to V_{ss}); V_{ss} = volume of steady state.

Results

A median of 11 blood samples per infant were collected from 22 evaluable propofol patients. The pharmacokinetics of propofol were best described with a two-compartment model. In some of the patients, the central line had not been primed, for which we added a lag time (ALAG) for a subpopulation to the model to describe the delay of delivery. Body weight (median, 8.9 kg) incorporated as a power function was found to be a significant covariate for elimination clearance, thereby reducing the interindividual variability (CV%) in clearance from 27% to 20%. A slope-intercept model or a weight-proportional model resulted in the same decrease in objective function. The addition of other covariates (arterial blood pressure, heart frequency, triglycerides, CYP isoforms [2B6*5, *6, *7, 2C9*2, 2C9*3, 2C19*2], age, body mass index, body surface area, and sex) to the model did not improve the quality of fit. The pharmacokinetic parameter values and precision of the basic model, the body weight power-adjusted model, and the values obtained from the bootstrapping are shown in table 2. The fits of 250 bootstrap replicates of the data set demonstrated the stability of the model. Individual fits of the model for a median situation and the most biased situation of the final model (body weight power model) to the observed data are shown in figure 1.

Simulations

The simulations using the pharmacokinetic model previously developed by Knibbe *et al.*,³ Rigby-Jones *et al.*,¹⁶ and Schüttler and Ihmsen¹⁷ overestimated the observed propofol concentrations in our patients (fig. 2), indicating that the pharmacokinetics in our study population of awake children are distinctly different.

Pharmacodynamics

The total data set included a median of 15 (3–25) COMFORT-B scores and 73 (3–101) BIS observations per infant from 21 propofol patients, 9 natural sleep patients who received no sedative, and 13 natural sleep patients until midazolam administration. Table 3 summarizes the estimated pharmacodynamic parameters for the full model (postoperative natural sleep pattern and propofol effect) for the COMFORT-B and the BIS. All infants arrived comfortable and lightly sedated at the PSICU (BSL), starting with a COMFORT-B score of 10.4 (CV 16%) and a BIS value of 79 (CV 7%). In the agitated infants during the postoperative night, the narcotic effect washed out earlier, indicated by a smaller $T_{50,PS}$ (518 *vs.* 1,580 min for the COMFORT-B and 1,044 *vs.* 2,052 min for the BIS). The steepness value of the washout effect (γ) for the BIS was 8, whereas the steepness for the COMFORT-B was not found to be significantly different from 1. During the night, the infants were “deeper” asleep, which was implemented in the model using the dip of a circadian rhythm. The start of the dip was estimated at 20:00 h (equal to 480 min from

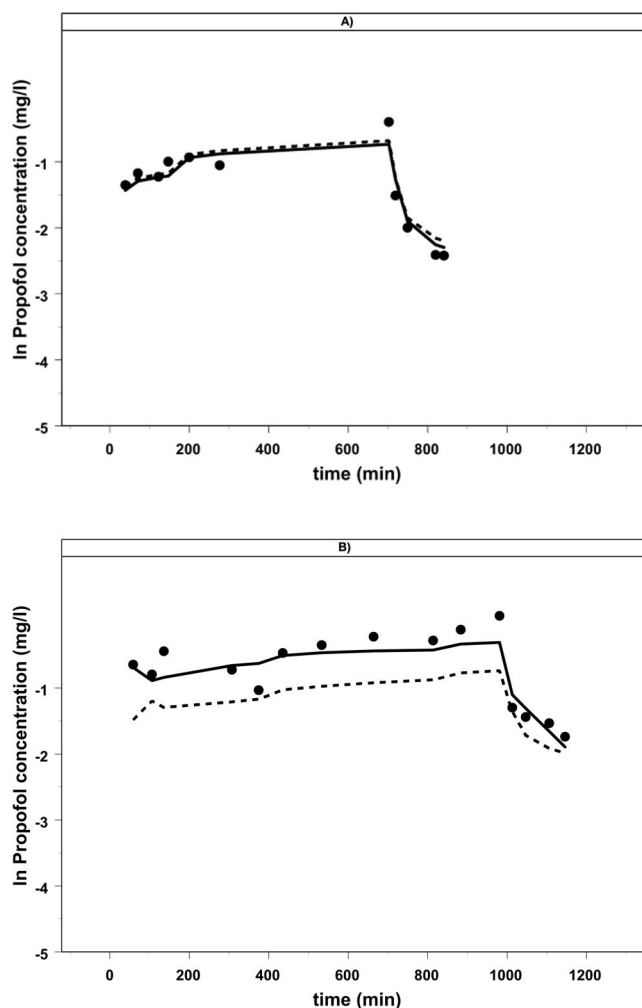


Fig. 1. Log-transformed propofol concentration *versus* time for a median (A) and the worst (B) performance of the final pharmacokinetic body weight power model. The solid circles represent measured propofol concentrations, the solid lines represent the individual predicted concentrations, and the dashed lines represent the population predicted concentrations.

12:00 h) on the COMFORT-B with an amplitude of 3.5 units and 17:30 h (equal to 330 min) on the BIS with an amplitude of 14.5. For the agitated infants receiving propofol during the night, a night dip could not be estimated. Propofol was started at a median time of 19:00 h, which is equal to 5.5 h after surgery. The induced BIS depression as a function of the propofol concentration showed considerable intersubject variability (CV 145%). The bootstrap validation (100 times) confirmed the precision of the parameters. Figure 3A shows a median fit of a nonagitated infant who received no sedative, with a reduction in response during the night. Figures 3B and C show a median and a worse fit of the sleep pattern of an agitated infant and the influence of propofol. Figure 4 illustrates the simulated relation among time, propofol infusion rate, propofol concentration, and predicted population response in terms of depth of sedation using COMFORT-B and BIS. The difference between a 10-kg infant and a 5-kg infant is shown at

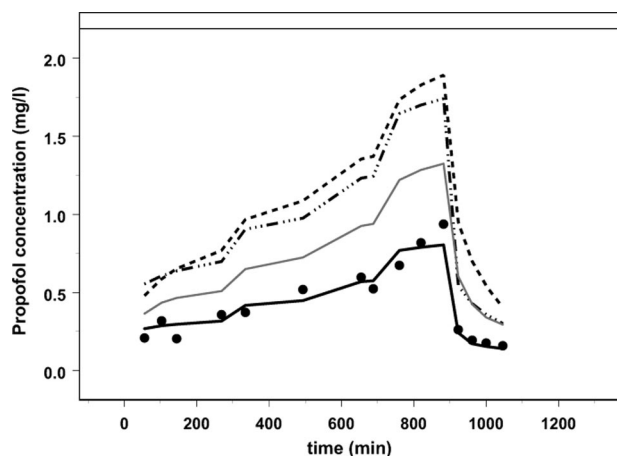


Fig. 2. Simulated population propofol concentrations (line) versus observed concentrations (solid circles) in an infant aged 10 months and weighing 10 kg, after continuous infusion of 18, 24, 30, and eventually up to 42 mg/h. The simulations were based on the current study (solid black line) and published pharmacokinetic models in ventilated children after cardiac surgery (dashed line)³ (dashed and dotted line)¹⁶ and during anesthesia (solid gray line).¹⁷

the infusion rate of 18 mg/h. The difference in postoperative natural sleep pattern between infants who did or did not become agitated is shown at the propofol infusion rate of 0 mg/h.

There was not enough evidence to support sex, age, body weight, and total dose of fentanyl during surgery as covariates on the pharmacodynamic parameters.

Discussion

To support safe and effective use of propofol during the first night after major surgery in nonventilated infants younger than 1.5 yr, a population model for the influence of propofol pharmacokinetics and pharmacodynamics on the depth of sedation was described, assessed using COMFORT-B and BIS.

Clearance in postsurgical healthy nonventilated infants was found to be two times higher than reported in the literature for ventilated children and adults.^{3,16,17} Based on the pharmacokinetic model, propofol doses must be doubled in this pediatric group to obtain similar blood concentrations. We believe that the higher estimate of the Cl (0.70 l/min) in an infant with a body weight of 8.9 kg (2.64 l/min standardized to an adult of 70 kg) in our study compared with 0.27 l/min ($0.030 \text{ l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) reported in the literature can be partly explained by the effect of the surgery and the condition of the patients. Rigby-Jones *et al.*¹⁶ found that patients aged 1 week to 12 yr undergoing cardiac surgery had reduced values for metabolic clearance (-26%). Cardiac patients in general show a reduced cardiac output, which may effect the propofol elimination because the clearance of propofol (a high-extraction drug) is dependent on liver blood flow. In addition, mechanical ventilation may be of influence on the clearance of propofol. In patients with trauma and those in the surgical intensive care unit, increasing the positive end-expiratory pressure during

Table 3. Pharmacodynamic Parameter Estimates of the Depth of Sedation Postoperatively Using COMFORT-B and BIS and the Stability of the Parameters Using the Bootstrap Validation

Parameter	COMFORT-B, Mean (%CV)	BS COMFORT-B, Mean (%CV)	BIS, Mean (%CV)	BS BIS, Mean (%CV)
Fixed effects				
BSL	10.4 (5.1)	10.4 (5.6)	79.2 (1.2)	78.9 (1.1)
PAEFF				
$T_{50,PS}$, min, agitated	518 (44.2)	548 (49.7)	1,044 (7.1)	1,048 (10.8)
$T_{50,PS}$, min, nonagitated	1,580 (46.3)	1,694 (49.9)	2,052 (24.3)	2,106 (41.5)
γ	1 Fixed	—	8.3 (27.3)	9.7 (46.3)
Maximal score S_{\max}	20.0 (25.1)	19.7 (28.5)	100 Fixed	—
CNR				
Onset, min	480 (1.2)	376 (42)	330 (0.8)	323 (11.8)
Frequency, min	1,390 (8.6)	1,752 (38.4)	2,440 (20.3)	2,796 (31.1)
Amplitude, response units	3.5 (36.7)	3.7 (33.7)	14.5 (16.2)	16.8 (18.7)
PEF				
EC_{50} , mg/l	1.76 (28.4)	2.01 (38.7)	3.71 (31.3)	4.01 (38.0)
Interindividual variability, %				
BSL	16 (33.6)	15 (37.1)	7 (22.7)	7 (18.9)
$T_{50,PS}$	—	—	23 (48.0)	29 (55.0)
γ	—	—	115 (48.3)	103 (65.9)
EC_{50}	47 (70.2)	47 (80.7)	145 (43.2)	135 (59.3)
Residual error				
ε_1 , %	32 (8.1)	32 (8.1)	—	—
ε_2 , BIS units	—	—	13 (6.0)	13 (6.5)
Performance measures				
$-2LL$	2,470.9	2,446	16,497	16,430

$-2LL$ = objective function; γ = steepness; ε_1 = residual error proportional; ε_2 = residual error additive; BIS = Bispectral Index; BS = bootstrap validation; BSL = level of sedation at arrival; COMFORT-B = COMFORT-Behavior score; CNR = circadian night rhythm; CV = coefficient of variation of the parameter values; EC_{50} = propofol concentration at half maximum effect; interindividual variability = square root of the exponential variance of η minus 1; PAEFF = postanesthesia effect; PEF = propofol effect; $T_{50,PS}$ = time postsurgery at half maximum postanesthesia effect.

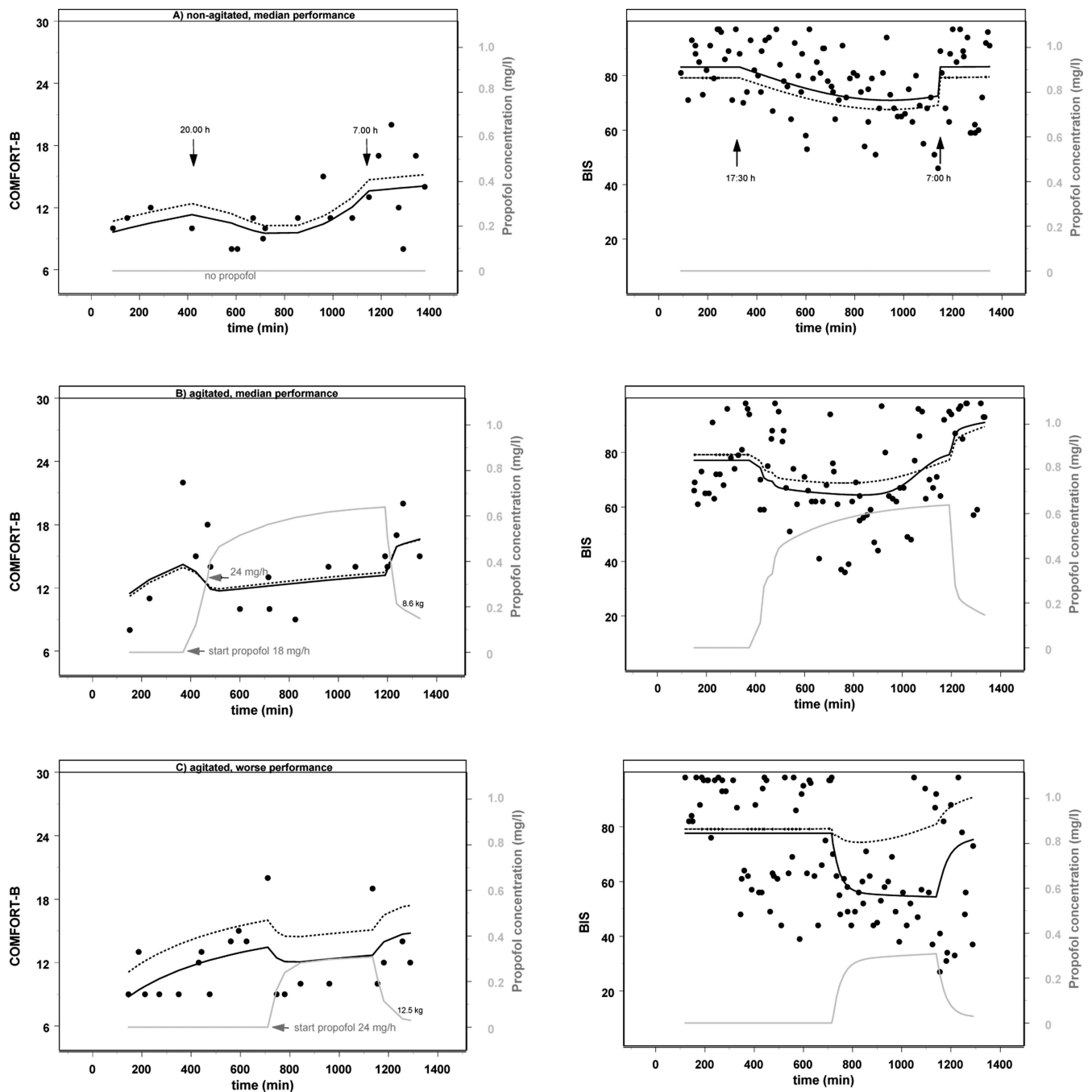


Fig. 3. COMFORT-Behavior score (COMFORT-B; *left column*) and Bispectral Index (BIS; *right column*) versus time (minutes) from 12:00 h for a median performance in the nonagitated group (A) and a median (B) and worse (C) performance in the agitated group receiving propofol. The *solid circles* represent the observations, the *solid lines* represent the individual predicted observations, and the *dashed lines* represent the population predicted observations. The *gray line* represents the individual predicted propofol concentrations.

mechanical ventilation has been shown to decrease total hepatic blood flow.¹⁸ Murat *et al.*² reported a large clearance of 0.44 l/min ($0.049 \text{ l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) in spontaneously breathing children aged 1–3 yr with minor burns after a single dose of 4 mg/kg. Healthy ventilated children undergoing anesthesia did show a lower estimate of the clearance.^{17,19} The model developed by Schüttler and Ihmsen¹⁷ for healthy ventilated children undergoing anesthesia from 2 yr of age showed less

overprediction of the blood concentration than the model developed by Knibbe *et al.*³ and Rigby-Jones *et al.*¹⁶ for ventilated children after cardiac surgery. They also found a smaller value of the central volume compared with our model (5–12 *vs.* 19 l), which may be a consequence of the relation of the central volume to the volume of distribution of steady state. Body weight partially explained the interpatient variability in Cl. The influence of a slope-intercept model, a proportional

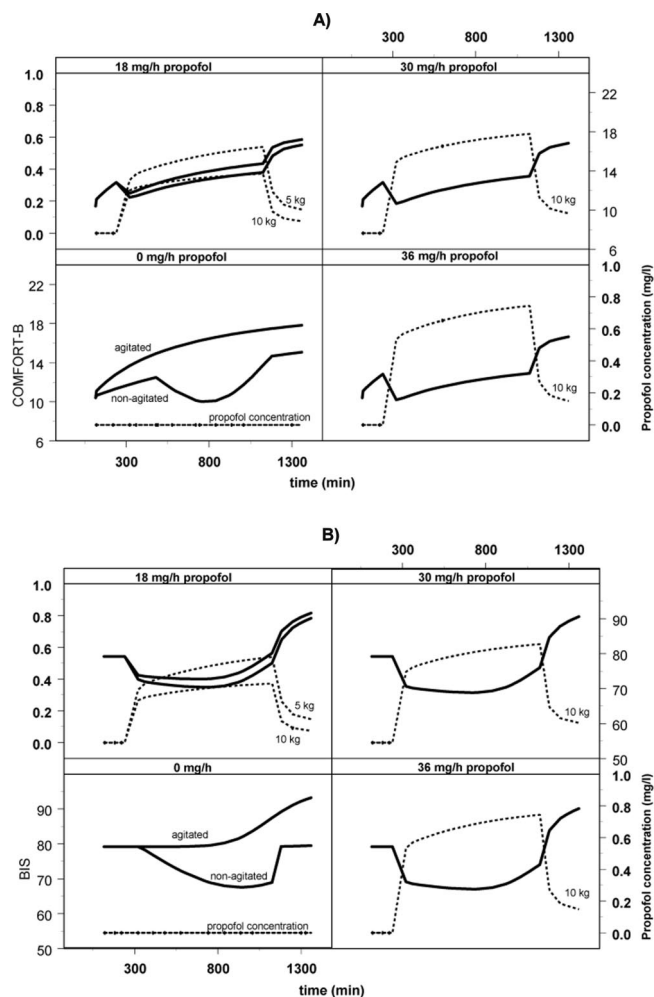


Fig. 4. Simulated representation of the relation between time (minutes) from 12:00 h, propofol administration (0, 18, 30, and 36 mg/h), population predicted propofol concentration (dashed line) and population predicted response COMFORT-Behavior score (COMFORT-B; A) and Bispectral Index (BIS; B) (solid lines) in a 10-kg and a 5-kg infant.

model, or a power model with a power scaling parameter of 0.61 on the clearance was comparable in the range of 4.8–12.5 kg. We choose the power model because an allometric three-fourths power model has been used with success for interspecies scaling.²⁰ As with other studies, age was not found to be a significant covariate.^{16,21} In addition, the genetic expression of the investigated CYP isoforms did not explain the interindividual differences in the clearance. 2B6 would be predominantly involved and, at a lower rate, 2C9 and 2C19 in the minor metabolic hydroxylation pathway.²² The homogeneous patient characteristics and the relatively small number of patients may account for the unexplained interpatient variability.

The large pharmacodynamic interindividual variability and residual error in BIS and COMFORT-B emphasize the complexity of depth of sedation in infants. Young children can vary in depth of sedation in the absence of sedatives as a result of day-night rhythm, the presence of parents and

medical staff, hunger, light, and noise.^{5,23} Especially at lighter sedation levels, noise has a greater effect on the BIS.²⁴ To account for natural variation, data of infants not receiving a sedative and until sedative administration were used to describe a postanesthesia effect (PAEFF) and a night dip (CNR). For adults, a similar PAEFF has been described after coronary artery bypass grafting by assuming a virtual drug that washes out over time.²⁵ Because stress and severe discomfort entail risks, a complete natural sleep pattern of agitated infants could not be described. The administration of the sedative may cover the night dip, which could not be estimated in the agitated children. The EC_{50} of propofol for the reduction of the BIS was different from that of the COMFORT-B, indicating that the two measurements are not interchangeable measures of the propofol effect in a spontaneously breathing child. Courtman *et al.*²⁶ and Crain *et al.*²⁷ also suggest that the BIS and COMFORT are only moderately correlated: A child can be comfortable but fully awake. The use of the BIS has the advantage that it assesses sedation continuously and may allow more objective assessment of sedation. It gives additive information and can be useful for patients who are difficult to assess clinically. The use of the maximal estimated score of 20 on the COMFORT-B scale and a smaller number of observations make it difficult to determine which sedation scale is more sensitive in this population based on the EC_{50} , but in lightly sedated children, the COMFORT-B seems more advantageous. The COMFORT-B has never been used before as a pharmacodynamic instrument in a pharmacokinetic-pharmacodynamic propofol analysis, but the effect of propofol on BIS in adults has been described. Interestingly, the sensitivity of infants to propofol, defined as EC_{50} , seems comparable to that in adults. Defining the E_{max} as the maximum effect seen on the BIS, Bouillon *et al.*²⁸ estimated an EC_{50} of 3.07 mg/l (CV 12.1%), and Doufas *et al.*²⁹ estimated a value of 2.4 mg/l (CV 30%). By fixing the E_{max} to 100, Calvo *et al.*³⁰ estimated the EC_{50} on 3.91 mg/l (41%), which may suggest that infants only require higher doses because of differences in pharmacokinetics rather than pharmacodynamics. In general, the sensitivity to propofol between infants is quite variable. Unfortunately, no explanation could be found based on patient characteristics as age, body weight and sex. In this narrow age group, the potential stressful environment resulting from inability to see, separation from parents, and unknown voices may play a major role.

Based on the population pharmacodynamic model, we advise a propofol infusion rate of 30 mg/h for a 10-kg nonventilated infant to achieve a COMFORT-B score between 12 and 14, 6 h after surgery during the night, which corresponds to BIS values of 70–75 (fig. 4). The considerable variability emphasizes the importance of drug titration to a maximum of $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Further pharmacodynamic studies in larger groups of children are needed to explain the variability in response and help clinicians to improve individualization. For drugs

such as propofol, this is especially important because of the troublesome reports in the literature regarding the safety of the use of propofol in children beyond procedures.

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