

Pharmacokinetic–Pharmacodynamic Modeling of Propofol in Children

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ABSTRACT

Background: The aim of this study was to identify the best model to describe pharmacokinetics and pharmacodynamics in prepubertal children and therefore to calculate the corresponding pharmacodynamic parameters. In addition, and to confirm our method, a group of postpubertal subjects was also studied.

Methods: Sixteen children (9.5 yr, range 6–12) and 13 adults (22 yr, range 13–35) were included. Induction was performed by plasma target-controlled infusion of propofol (6 $\mu\text{g}/\text{ml}$) based on the Kataria model in children and on the Schnider model in adults. The relationship of bispectral index to predicted concentrations was studied during induction using the Kataria, pediatric Marsh, Schüttler, and Schnider models in children. Because the best performance was obtained, strangely enough, with the Schnider model, the two groups were pooled to investigate influence of puberty on pharmacodynamic parameters (k_{E_0} [plasma effect-site equilibration rate constant] and $C_{E_{50}}$ [effect-site concentration corresponding with 50% of the maximal effect]). The time-to-peak effect was calculated, and the k_{E_0} was determined for the Kataria model (nonlinear mixed-effects modeling; pkpdttools).

Results: In children, the predicted concentration/effect relationship was best described using the Schnider model. When the whole population was considered, a significant improve-

ment in this model was obtained using puberty as a covariate for k_{E_0} and $C_{E_{50}}$. The time to peak effect, T_{peak} (median, 0.71 [range, 0.37–1.64] and 1.73 [1.4–2.68] min), and the $C_{E_{50}}$ (3.71 [1.88–4.4] and 3.07 [2.95–5.21] $\mu\text{g}/\text{ml}$) were shorter and higher, respectively, in children than in adults. The k_{E_0} linked to the Kataria model was 4.6 [1.4–11] min.

Conclusions: In children, the predicted concentration/effect relationships were best described using the Schnider model described for adults compared with classic pediatric models. The study suggests that the Schnider model might be useful for propofol target-control infusion in children.

What We Already Know about This Topic

- ❖ Despite use of propofol in children, its pharmacokinetic and dynamic relationships have been inadequately explored

What This Article Tells Us That Is New

- ❖ In 16 prepubertal children receiving propofol for middle ear surgery, the predicted concentration/effect relationships were better described by an adult model (Schnider model) than by a classic pediatric model

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DESPITE its common usage in adults, propofol anesthesia remains infrequently used in children. Traditionally, most pediatric anesthesiologists have preferred to use inhalational anesthesia, which is easy to administer and allows smooth induction and rapid recovery. During the last few years, however, propofol anesthesia has been demonstrated to offer some clinical advantages compared with inhalational anesthesia; indeed, propofol anesthesia causes less postanesthetic nausea and vomiting¹ and less emergence agitation.^{2,3} In addition, some concerns have been raised regarding the electroencephalographic epileptoid signs associated with high sevoflurane concentrations. Continuous propofol infusion now seems to be an interesting alternative to inhalational anesthesia in children, and its use is likely to increase. Optimal continuous propofol intravenous administration requires knowledge of pharmacokinetic-pharmacodynamic (PK-PD) profiles to predict not only changes in blood concentrations of the drug (pharmacokinetic domain) but also changes of the desirable effect (pharmacodynamic domain). However, childhood is a period of multiple physiologic maturations, including variations in body composi-

tion regarding fluid, muscle, and fat proportions and variations in metabolic capacities; these maturational changes lead to age-dependence of distribution volumes and clearances. In addition the speed of physiologic maturation, specific to each child, tends to increase interindividual variability of the PK-PD profile in the pediatric population. These specific pediatric circumstances may make the mathematical modeling uncertain and thus may explain the poor predictability of most of the published pharmacokinetic models.⁴ As demonstrated in adults, targeting an effect-site concentration (C_e) allows more rapid control of depth of anesthesia, especially during short procedures or surgical procedures with a variable level of stimulation.⁵ In children, however, pharmacodynamic parameters are still debated, and no PK-PD models are currently available. The bispectral index (BIS), an electroencephalography-based monitor of depth of anesthesia, provides reliable clinical feedback of the propofol cortical effect in children as in adults.^{6,7}

Provided an adequate measurement tool for drug effect exists, the time to peak effect (T_{peak}), a model-independent pharmacodynamic parameter,⁸ can be determined for each patient using a nonlinear mixed-effects modeling (NONMEM) approach.

Using the BIS as pharmacodynamic feedback, the aim of this study was to identify, among a set of models, the model that most appropriately describes the pharmacokinetics and the pharmacodynamics in prepubertal children and thereby calculate the corresponding pharmacodynamic parameters using the NONMEM approach. In addition, and to confirm our method, a group of postpubertal subjects was also studied.

Materials and Methods

Patients

After Institutional Review Board (Saint-Antoine, Paris, France) approval and informed consent either from the children and their parents or from the adult patients, 29 patients (6 to 35 yr; American Society of Anesthesiologists physical status I or II) scheduled for middle-ear surgery were included in the study. They were allocated either to the prepubertal group (children, $n = 16$) or to the postpubertal group (adults, $n = 13$) according to the clinical observation of external secondary sex characteristics (Tanner Stage 4).⁹ Patients were excluded if they received preoperative drugs that altered the electroencephalogram.

Study Design

All patients received oral hydroxyzine (1 mg/kg) 1 hr before surgery as a premedication. Before induction, a venous catheter was placed for fluid infusion and drug administration. Propofol target-controlled infusion (TCI) system consisted in an Alaris[®] PK infusion pump (Cardinal Health, Dublin, OH) driven by the RUGLOOP software (Demed Engineering, Temse, Belgium).^{10,11}

In prepubertal patients (children), TCI was based on the Kataria model,¹² a weight-proportional model with age as an

additional covariate for the rapid distribution compartment. In the postpubertal group (adults), the Schnider model was used.¹³ This model was chosen because it was validated prospectively and has given an acceptable bias.¹¹ In addition, this model integrates age and lean body mass as covariates and could therefore be a relevant model to use when administering propofol to young adults, such as our postpubertal population ranging from 13 to 35 yr.

In all patients, a standardized induction was performed with a propofol plasma target concentration of 6 $\mu\text{g}/\text{ml}$ for 8 min. During induction, propofol was administered alone. At the end of induction, a single dose of atracurium (0.5 mg/kg) was administered to facilitate tracheal intubation. A remifentanyl infusion was initiated at 0.25 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ after tracheal intubation and was kept constant throughout the case to counteract surgical stimuli. From tracheal intubation to the end of surgery, propofol plasma target concentration was set to reach and maintain a BIS value between 40 and 60 using the RUGLOOP software as described above.

After the end of surgery, the remifentanyl was stopped and two steady-state 10-min periods were obtained in each patient at two different estimated propofol concentrations randomly assigned (2, 3, 4, 5, or 6 $\mu\text{g}/\text{ml}$). At the end of each stable 10-min period, venous blood samples were drawn to measure propofol blood concentration.

In addition to standard monitoring, a disposable BIS-Sensor[®] XP (Aspect Medical Systems, Norwood, MA) was applied to the forehead of each patient before induction of anesthesia and connected to a BIS[®] monitor Cardiacap II (Datex-GE Healthcare, Helsinki, Finland). The adult sensor was used for all patients. The skin was prepared to ensure low impedance and a good quality signal. The smoothening rate of the BIS monitor was set at 15 s. During the study, the data were recorded continuously, with a sample rate of 4 Hz, using the RUGLOOP II software loaded into a dedicated microcomputer (Demed Engineering).

These data included (1) standard monitoring such as non-invasive blood pressure, heart rate, peripheral oxygen saturation, and expired gases; (2) infusion parameters with predicted plasma concentrations; and (3) BIS and associated values such as index quality signal, suppression ratio, and electromyographic activity. Blood samples were immediately centrifuged, and plasma was stored at -40°C until analysis. Quantification of propofol was performed by high-performance liquid chromatographic technique as described previously by Knibbe *et al.*¹⁴

Pharmacodynamic Modeling

The relationship between BIS and predicted propofol concentrations was investigated on preintubation data, when propofol was administered alone and no stimulation took place, assuming the effect site to be a compartment of trivial volume linked to the plasma by a first-order plasma effect-site equilibration rate constant, k_{E0} , and using a classic sigmoid E_{max} model: $\text{Effect} = E_0 + (E_{max} - E_0) \cdot (C_e^\gamma / (C_e^\gamma + C_e^\gamma))$, where Effect is the recorded BIS, E_0 is the baseline BIS

Table 1. Lag Time and Pharmacokinetic Parameters Calculated with NONMEM in Children, Using the Kataria Model

Lag Time	OF	kE ₀	P kE ₀ (%)	Ce ₅₀	P Ce ₅₀ (%)
0	10,316	6.459	86	4.082	95
15 s	10,396	6.560	86	3.315	96
30 s	10,360	2.715	91	1.933	99
35 s	10,298	2.909	91	1.580	99
37 s	10,266	3.055	91	1.433	99
40 s	10,222	3.420	88	1.241	100
42 s	10,185	3.800	87	1.096	99
43 s	10,168	4.124	84	1.017	99
44 s	10,158	4.516	84	0.951	99
45 s	10,160	4.647	81	0.919	99
47 s	10,130	7.192	76	0.849	99
50 s	10,135	12.112	65	0.682	99
60 s	10,395	19.967	54	—	100

Ce₅₀ = concentration inducing 50% of the maximal effect; kE₀ = plasma effect-site equilibration rate constant; NONMEM = nonlinear mixed-effects modeling; OF = objective function; P Ce₅₀ = probability for the Ce₅₀ value to correspond to reality; P kE₀ = probability for the kE₀ value to correspond to reality.

measurement when no drug is present, E_{\max} is the maximum possible propofol effect (BIS = 0), Ce is the calculated effect-site propofol concentration, Ce₅₀ is the Ce associated with 50% maximal drug effect, and γ is the steepness of the concentration-*versus*-response curve. The model parameters were estimated using NONMEM VI (GloboMax LLC, Hanover, MD) as follows.

The population characteristics of the pharmacokinetic parameters (fixed and random effects) were estimated using the subroutine ADVAN6 from the library of programs provided with the NONMEM-PREDPP package, with three

Table 2. Lag Time and Pharmacokinetic Parameters Calculated with NONMEM in Children, Using the Schnider Model

Lag Time	OF	kE ₀	P kE ₀ (%)	Ce ₅₀	P Ce ₅₀ (%)
0	10,250	0.710	99	4.161	100
15 s	10,186	0.877	99	3.563	100
30 s	10,092	1.164	98	2.744	99
35 s	10,037	1.435	95	2.459	100
37 s	10,008	1.570	95	2.331	100
40 s	9,967	1.828	94	2.131	99
42 s	9,938	2.103	92	1.971	100
43 s	9,927	2.400	91	1.910	100
44 s	9,919	2.813	92	1.847	100
45 s	9,920	2.631	89	1.799	100
47 s	9,894	3.615	85	1.668	100
50 s	N.M.	—	—	—	—
60 s	N.M.	—	—	—	—

Ce₅₀ = concentration inducing 50% of the maximal effect; kE₀ = plasma effect-site equilibration rate constant; N.M. = no minimization; NONMEM = nonlinear mixed-effects modeling; OF = objective function; P Ce₅₀ = probability for the Ce₅₀ value to correspond to reality; P kE₀ = probability for the kE₀ value to correspond to reality.

pharmacokinetic compartments and one effect compartment. The pharmacokinetic parameters were those of published models with a fixed value. The pharmacodynamic parameters transfer rate constant of the effect (kE₀), Ce₅₀, and γ were calculated. For Ce₅₀ and kE₀, interindividual variability was permitted and estimated using the exponential error model $P_i = P_{TV} \cdot e^{-\eta_i}$, where P_i is the value of the parameter for the i^{th} patient, P_{TV} is the typical population value of the parameter, and η is a random variable with a mean of 0 and a variance of ω .² Individual variability is reported as ω , the SD of η in the log domain, which is approximately the coefficient of variation in the standard domain. Residual intra-individual variability was modeled using a standard additive error model. The estimation step used the first order conditional estimation with interaction. Empirical Bayes estimates of pharmacodynamic parameters for each subject were obtained using the POSTHOC option in NONMEM.

In a first step, the relationship between BIS and predicted concentrations was analyzed separately in the two groups: in the children group using successively Kataria,¹² pediatric Marsh,¹⁵ Schüttler,¹⁶ and Schnider¹⁷ models and in the adult group using the Schnider model.¹⁷

Several studies¹⁸ have stressed the importance of taking into account the lag time between the actual electroencephalographic status of the patients and the value displayed on the monitors.¹⁹ This delay may reflect the combination of the averaging algorithm to calculate the BIS and the delay in adaptation of one of the artifact-rejection processing steps.²⁰ Thus, NONMEM was run using a lag time value for BIS of 0, 15, or 30 s, and the improvement of the model was estimated based on a reduction of the minimum objective function (OF) ($-2 \log$ likelihood). When the change of the lag time resulted in an OF decrease of at least 4 units, it was considered significant ($P < 0.05$) and included in the model. NONMEM provides several criteria for the adequacy of the “best” model. An obvious one is the OF, which corresponds to -2 times the log of the likelihood.

This OF is minimized during the optimization process, and the model with the lowest OF is considered the best one. Nevertheless, NONMEM also provides a probability for any parameter value to correspond to reality, given the null hypothesis that the true arithmetic mean of the η estimates is zero. Consequently, we decided to retain as the adequate lag time a value superior to 15 s (smoothing time), which gives a probability of at least 95% for the kE₀ value to correspond to reality. This 95% probability was never reached with the Kataria model; as can be seen in tables 1 and 2, however, 30 s seems to be a good compromise between OF value and kE₀ estimation. The OF actually decreases down to 50 s with the Kataria model (minimization fails at 50 and 60 s with the Schnider model), but with such lag times, the estimation of kE₀ is clearly defective.

In a second step, the two groups were pooled, and the relationship was analyzed for the whole population with Schnider's model to investigate the influence of puberty status as a covariate on pharmacodynamic parameters (kE₀, Ce₅₀).

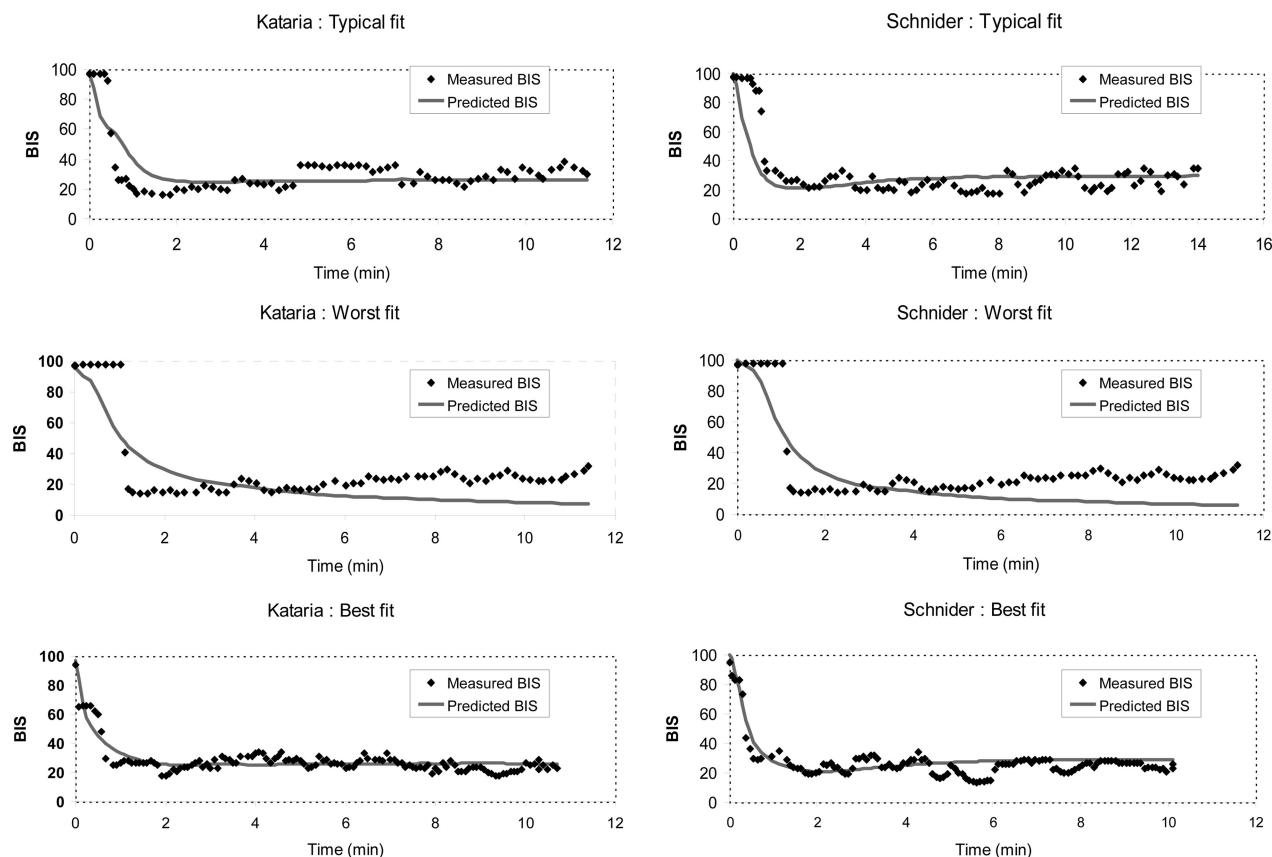


Fig. 1. Average, best, and worst fits with the bispectral (BIS) curve observed under the pharmacokinetic parameters of the Kataria and Schnider models with 30-s lag time.

Here again, the introduction of the new covariate was considered significant if it led to an OF reduction of at least 4 units.

The T_{peak} was calculated for all patients from the *post hoc* values estimated by NONMEM, using pkpdttools, developed by Charles Minto and Thomas Schnider.[§] T_{peak} values calculated within the two groups were compared using the Mann–Whitney U test. Assuming the independence of T_{peak} from the pharmacokinetic model,⁸ a kE_0 value calculated with the Kataria model to yield the same T_{peak} was estimated in the children group.

Performance of the Models

The models' pharmacodynamic performance was estimated by calculating the prediction error between measured (BIS_{meas}) and predicted BIS (BIS_{pred}) values recorded during induction as $PE = (BIS_{\text{meas}} - BIS_{\text{pred}})/BIS_{\text{pred}}$. This allowed calculation of the bias (median performance error) and imprecision (median of absolute values of performance errors) for each patient. The quality of the fit over time was also visually assessed by plotting, in each subject, the measured/predicted values as a function of time. This was further illustrated by displaying, for the Kataria and Schnider models, the best, average, and worst fit (fig. 1).

Considering the whole infusion profile, predicted plasma propofol concentrations were estimated in children with the Kataria and the Schnider models at the time of blood sampling performed under steady-state conditions. These estimates were then compared with the actual measured values to obtain the performance of both pharmacokinetic models in the children group: median performance error, median of absolute values of performance errors, and wobble.

Statistical Analysis

Based on T_{peak} data published previously, a prospective power analysis was done before initiation of the trial. We calculated group size according to an expected T_{peak} difference of 40% between adults and children, with an SD of difference of 35%²¹; we estimated that a minimum of 10 subjects was required per group ($\alpha = 0.05$ and $\beta = 0.2$).

Differences between children and adults were investigated using ANOVA and nonparametric tests (Kolmogorov–Smirnov [Statview version 4.57 for Windows; Abacus Concepts Inc., Berkeley, CA]) as appropriate. T_{peak} calculated within the two groups was compared using the Mann–Whitney U test. Regarding the assessment of the model performances, the potential influence of age, amount of remifentanyl, amount of propofol, and level of targeted concentrations on the accuracy of predicted concentrations was tested using

§ <http://www.pkpdttools.com>. Accessed June 18, 2010.

Table 3. Population Data and Induction Characteristics

Characteristic	Children	Adults
Patients, No.	16	13
Age (yr)	9.5 ± 2.5*	22 ± 8
Sex (male/female)	11/5	6/7
Body mass index	17.0 ± 1.8*	22.0 ± 2.3
BIS value at baseline	95.8 ± 2	95.8 ± 3
BIS value at tracheal intubation	29 ± 7	27 ± 4
Propofol consumption during induction (mg/kg)	9.7 ± 1*	5.3 ± 0.8

Data are presented as mean ± SD.

* $P < 0.001$, children vs. adults.

BIS = bispectral index.

Pearson's correlation. A value of $P < 0.05$ was considered significant.

Results

Demographic and anesthetic data are shown in table 3. The youngest child was 6 yr old and the oldest adult was 35 yr old. In the children group, the best fit for the analysis of the predicted concentration/BIS relationship was obtained with the Schnider model. The three pediatric models initially considered for the analysis (Kataria, pediatric Marsh, and Schüttler) were less efficient in describing the predicted concentration/effect relationship (table 4).

Introducing a 15-s lag time did not significantly modify the NONMEM OF in any model, whereas introducing a 30-s lag time significantly improved all the models. Median performance error and median of absolute values of performance errors were estimated from the best models (lag time, 30 s).

In the adult group, the predicted concentration-*versus*-BIS relationship was well described using the Schnider model, and the pharmacodynamic parameters calculated were in the same range as those previously published in adult studies (table 5). Taking into account this unexpected result in the children group, we decided to perform a new analysis of the predicted concentration/BIS relationship in the whole population, pooling adults and children, which allowed us to

Table 5. Results of the NONMEM Pharmacodynamic Analysis in the Adult Population

Parameter	Schnider Adult Patients
OF with 0 lag time	9,784
OF with 30-s lag time	9,327
MDPE (%)	2.24
MDAPE (%)	14.23
kE_0 (range)	0.375 (0.14–0.63)
CV (%)	38%
Ce_{50} (range)	3.83 (2.95–5.21)
CV (%)	15%

kE_0 and Ce_{50} values are given as population value (range of individual estimated values).

Ce_{50} = concentration inducing 50% of the maximal effect; CV = coefficient of variation; kE_0 = plasma effect-site equilibration rate constant; MDAPE = median absolute performance error; MDPE = median performance error; NONMEM = nonlinear mixed-effects modeling; OF = objective function.

demonstrate that the pubertal status was a significant covariate in the model (table 6). The T_{peak} calculated with pkpdttools from this model was 0.71 [0.37–1.64] min (median [range]) in the children and 1.73 [1.4–2.68] min in the adults. The T_{peak} was significantly shorter in children ($P < 0.001$).

The initial analysis had not permitted us to adequately estimate kE_0 with the Kataria model (table 4). Therefore, the calculation of the kE_0 value to be linked to the Kataria model to yield the same T_{peak} was found to be 4.6 [1.4–11] min in the children group. The pharmacokinetic predictive performances of the Kataria and Schnider models evaluated in the children group from the plasma concentrations showed a poor predictability and a wide interindividual variability for both models (table 7). For both models, the bias was correlated with neither age, total amount of propofol administered, nor total amount of remifentanyl; whatever the model, our results demonstrated an increasing error as the concentration increased (fig. 2).

Discussion

Using a NONMEM approach, we have investigated the relationship between BIS and predicted propofol concentra-

Table 4. Results of the NONMEM Pharmacodynamic Analysis in the Children Population with Different Pharmacokinetic Models

Parameter	Kataria	Marsh	Schüttler	Schnider
OF with 0 lag time	10,322	10,626	10,725	10,251
OF with 30-s lag time	10,079	10,224	10,239	9,795
MDPE (%)	1.91	−1.57	0.00	−1.73
MDAPE (%)	19.1	21.8	22.0	21.0
kE_0 (range)	2.73 (0.48–15.60)	2.62 (0.48–13.30)	2.83 (0.48–63.10)	1.17 (0.28–4.51)
CV (%)	85	83	110	67
Ce_{50} (range)	1.99 (0.91–3.92)	6.88 (3.28–15.50)	4.11 (2.09–9.74)	2.64 (1.57–5.15)
CV (%)	31	35	36	35

kE_0 and Ce_{50} values are given as population value (range of individual estimated values).

Ce_{50} = concentration inducing 50% of the maximal effect; CV = coefficient of variation; kE_0 = plasma effect-site equilibration rate constant; MDAPE = median absolute performance error; MDPE = median performance error; NONMEM = nonlinear mixed-effects modeling; OF = objective function.

Table 6. Results of the NONMEM Pharmacodynamic Analysis in the Whole Population

Parameter	Schnider Whole Population
OF	
Without covariate	13,577
With "pubertal status" as a covariate on kE_0	13,541
With "pubertal status" as a covariate on Ce_{50}	13,573
With "pubertal status" as a covariate on both	13,537
MDPE (%)	5.49
MDAPE (%)	17.03
kE_0	
Adults (range)	0.272 (0.08–2.03)
Children (range)	1.770 (0.41–5.7)
CV (%)	57.5
Ce_{50}	
Adult (range)	3.07 (2.95–5.21)
Children (range)	3.71 (1.88–4.4)
CV (%)	21.4

kE_0 and Ce_{50} values are given as population value (range of individual estimated values).

Ce_{50} = concentration inducing 50% of the maximal effect; CV = coefficient of variation; kE_0 = plasma effect-site equilibration rate constant; MDAPE = median absolute performance error; MDPE = median performance error; NONMEM = nonlinear mixed-effects modeling; OF = objective function.

tions in children and young adults receiving propofol TCI. The first finding of this study was that in a pediatric population (6–13 yr), the best fit was obtained with the Schnider model, initially built up in an adult population. The Kataria, Marsh, and Schüttler models, for which pediatric versions are available, were less efficient in describing the predicted concentration/effect relationship. In addition, the incorporation of a new covariate (puberty status) improved the accuracy of the Schnider model in overall population including subjects from 6 to 35 yr. The second finding, drawn from the ability of the Schnider model to accurately describe the predicted concentration/BIS relationship in children and adults, was that pharmacodynamic parameters calculated were relevant with those previously published: in the children group, as expected, values obtained for T_{peak} and Ce_{50} were shorter and higher, respectively, compared with the values in adults,

Table 7. Pharmacokinetic Predictive Performances of Kataria and Schnider Models Evaluated in the Children Group from the Plasma Concentrations

Parameter	Schnider	Kataria
MDPE (%)	44.3 (3.8–117.9)	52.5 (12.5–97.1)
MDAPE (%)	44.3 (3.8–117.9)	52.5 (12.5–97.1)
Wobble (%)	13.8 (0.7–64.2)	13.4 (1.0–60.0)

Data are expressed as median (range).

MDAPE = median absolute performance error; MDPE = median performance error.

whereas in the adult group, these pharmacodynamic parameters were similar to those published previously.¹⁷

Regarding the description of the relationship between BIS and propofol concentrations, our unexpected first finding probably derives from the inability to describe precisely the initial distribution phase in the few pediatric pharmacokinetic studies available because of difficulties in obtaining early blood samples in this population. This might explain the important differences between the different models concerning the estimation of the volume of the central compartment.

The first attempt at pediatric modeling for continuous propofol infusion in children was conducted by Marsh *et al.*¹⁵ in a reexamination of a model first calculated in adults. The pediatric Marsh model, determined in 10 children, resulted from venous blood samples taken over 10 min after the initial bolus. Compared with adults, the volume of the central compartment in the Marsh pediatric model remains a linear function of body weight but is increased by approximately 50%.

When Kataria *et al.*¹² developed a three-compartment model in a population of children between the ages of 3 and 11 yr, they calculated a larger central compartment volume than that calculated by Marsh *et al.* By comparison, Kataria *et al.* performed more frequent and earlier samples: a first venous sample at T_0 ; sample intervals every 1.5 min after the end of induction dose then increased to every 2 min; and sample intervals finally increased to every 15–30 min. The authors demonstrated that implementation of the model with age as an additional covariate of distribution volume (V_2) has a weak influence on the performance of the model.

Schüttler *et al.*¹⁶ analyzed data and samples from several propofol pharmacokinetic studies performed in adults and children from 2 to 88 yr of age and built a model that incorporates age and weight as covariates for volumes and clearances: the inclusion of age and weight covariates in this inhomogeneous population significantly improved the model.

Basically, these previously published pediatric models are characterized by larger central compartments and higher rates of clearance, mainly in a weight-proportional manner for the Marsh and Kataria models and with a nonlinear dependence with weight and age for Schüttler model. To our knowledge, up to now, there have been no publications of prospective studies of the predictive performance of these models except for the study of Absalom *et al.*, which might be considered a pediatric validation of the Schüttler model.²²

In our study using the NONMEM approach provided by the package NONMEM-PREDPP, we failed to fit with relevance the predicted concentration/BIS relationship in our population of prepubertal children. The variability of concentrations after the bolus injection of propofol, an intrinsic property of the drug,²³ is amplified by the wide physiologic variability in our pediatric population. This increased variability may explain, at least in part, the failure of modeling of relationship between effect (BIS) and propofol concentrations predicted by the tested pediatric models in which the initial phase of distribution might be insufficiently described.

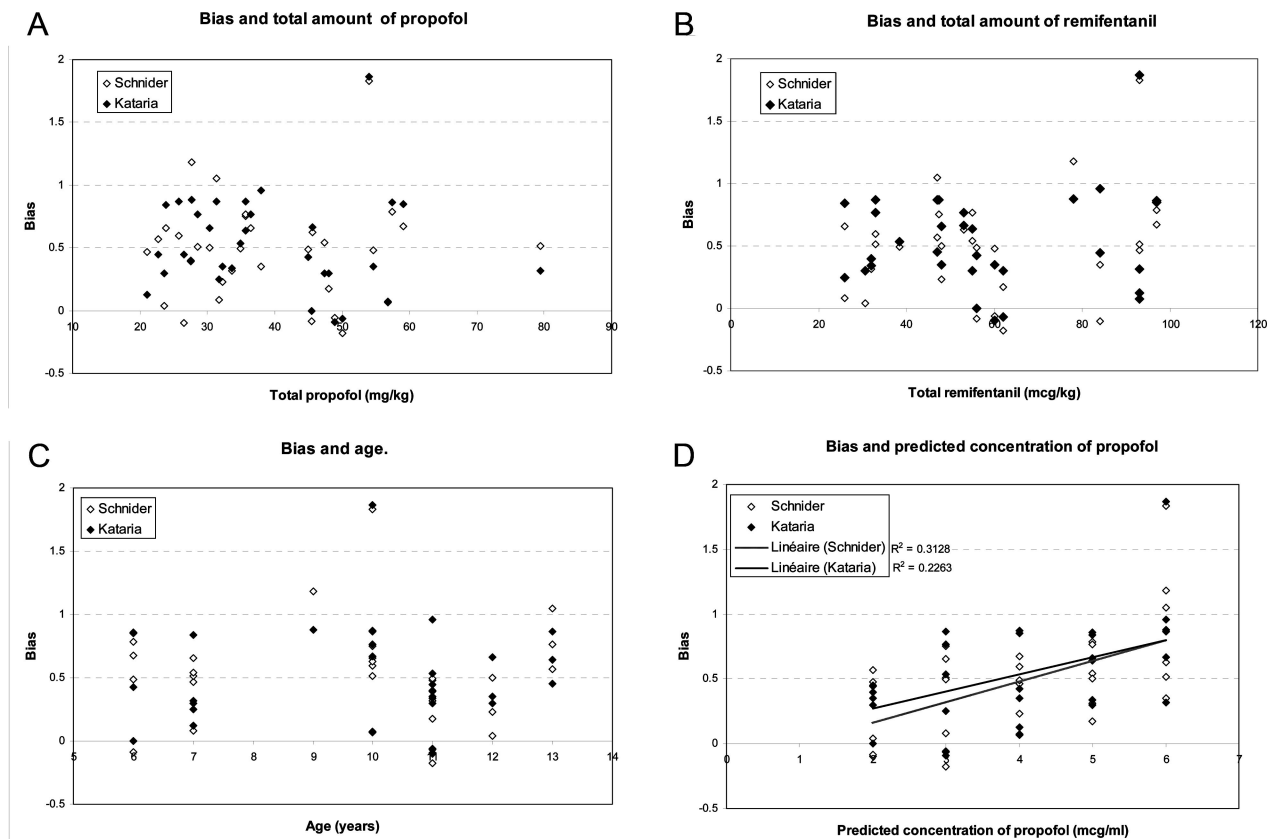


Fig. 2. Plots of the bias calculated with the Schnider model (white diamonds) or the Kataria model (black diamonds) versus the amount of propofol (A), the amount of remifentanyl (B), the age (C), and the level of predicted concentrations of propofol (D). Using the Kataria or the Schnider model, the bias was not correlated to the amount of propofol or remifentanyl administered or to the age. On the other hand, the bias increased with the predicted concentration of propofol with both models (Kataria, $P < 0.01$; Schnider, $P < 0.01$).

In view of these poor results, we investigated in our pediatric population the ability for the Schnider model, used in our adult population, to fit the predicted concentration/BIS relationship. Our unexpected results revealed an improvement in the OF associated with calculation of pharmacodynamic parameters such as kE_0 and Ce_{50} .

As opposed to pediatric models, the Schnider model is characterized by a fixed central compartment volume of distribution and includes many covariates: age in the rapid intercompartmental clearance and weight; height and lean body mass as covariates in the elimination clearance. In addition, in the study by Schnider *et al.*,¹³ performed in adults, early arterial blood samples were drawn during the initial distribution phase, after the bolus induction (five samples during the first 10 min), and sampling was extended up to 600 min after induction (more than 20 samples per patient). These numerous samples may have contributed to a more reliable description of the initial distribution phase compared with available pediatric studies.

Growth and maturation are two major aspects of children that are not seen in adults. The important interindividual variability that characterizes the children group may be investigated using covariates as weight, age, and height in PK-PD modeling. In addition, the particular importance of

including physiologic covariables, such as age and size in pediatric PK-PD models, to describe metabolic processes during growth and maturation is in agreement with numerous allometric scaling works in children.^{24–26} Indeed, the allometric method allows delineation of the age-dependent covariate effect from the effect of size. It has recently been demonstrated that metabolic clearance of propofol calculated with the allometric at 75% power reaches adult rates at approximately 50 weeks of age.²⁴ Consequently, from this age, metabolic rate may be considered proportional to geometric constraints of body size. Our results are consistent with these findings; indeed, in our study, the Schnider model, which incorporates age and lean body mass in intercompartmental and elimination clearances, described the time course of propofol better than weighted base (*i.e.*, per kilogram) clearance models. When growth curves are analyzed, a smooth transition is observed at 5 yr for height-for-age, weight-for-age, and body mass index-for-age, and these curves become more linear from 6 yr to puberty.²⁷ In addition, the relative importance of intercompartmental and metabolic clearances, compared with the central compartment, to describe the initial distribution of propofol may then partly explain the best fit obtained for the predicted concentration/effect relationship in our study when using

the Schnider model, a model with a fixed volume of the central compartment. The high median age in the children group of our study, 9.5 yr (6–13), may also possibly explain our results, suggesting the possible use of Schnider model for children older than 6 yr.

Using the T_{peak} method described by Minto *et al.*,⁸ we calculated the kE_0 of propofol for the children group with the Schnider model and found, as expected, an increased kE_0 value compared with adults. The effect-site concentration describes the evolution of a drug effect. Consequently, whatever the method of propofol administration, the estimate of the effect-site concentration is the only one that allows prediction of the effect. Several studies have demonstrated that a TCI device that controls the concentration at the effect site more precisely produces a desired time course of drug effect than a device that controls only plasma concentration.^{5,10,28}

Indeed, the predicted effect site propofol concentration is considered a more useful and reproducible indicator of depth of anesthesia than the predicted blood propofol concentration.²⁹ To directly target the effect-site compartment, the rate constant of equilibration between blood and effect-site (kE_0) has to be determined either at the same time as the pharmacokinetic model (PK-PD studies) or through a pharmacodynamic study leading to its link with a given pharmacokinetic model.

In our study, using the BIS, we determined the time to maximum cortical cerebral effect after a bolus dose of propofol in children as in adults. We demonstrated a shorter T_{peak} and a higher Ce_{50} in children compared with adults. These results support recent findings in a pediatric pharmacodynamic study performed by Jeleazcov *et al.*⁶ in which pharmacodynamic parameters (time to peak effect, kE_0 , and Ce_{50}) were found to be age-dependent. Indeed, in a population ranging in age from 1 to 16 yr, these authors describe an increasing T_{peak} and a decreasing kE_0 with age. Our results are also in accord with a previous study in which children showed higher EC_{50} of propofol than adults.³⁰ The influence of age on the sensitivity to propofol has already been suggested in adults: using the same clinical or electroencephalographic profile target, the required propofol concentration decreases with increasing age.¹⁷

On the contrary, in a recent work, Muñoz *et al.*²¹ found a longer propofol T_{peak} in children compared with adults. However, in that study, the maximal cerebral effect was estimated visually from a signal derived from auditory evoked potentials provided by the derived auditory evoked potential index monitor; in addition, the pharmacokinetic parameters used for TCI were based on the Paedfusor model for children and Marsh model for adults. These methodologic features were very different from our study design, rendering comparison with our results hazardous. Moreover, a recent study from the same team demonstrated that the BIS is more adapted to assess effect site than AEP monitor index in children receiving TCI of propofol.³¹

The T_{peak} is a useful pharmacodynamic parameter to combine pharmacokinetics and pharmacodynamics.¹⁰

Minto *et al.*⁸ demonstrated that T_{peak} can be used to link separate pharmacokinetic and pharmacodynamic studies. Indeed, as a model-independent parameter, T_{peak} can be used with different pharmacokinetic models to describe the time course of a drug effect in a given population. For a pharmacokinetic model, the correct kE_0 value is that which predicts the correct time of peak effect after submaximal doses. When a pharmacokinetic model is used and the T_{peak} for that drug and population is known, that T_{peak} can be used to calculate a unique kE_0 for each patient. Therefore, using the T_{peak} method in our pediatric population after PK-PD modeling, we calculated the kE_0 for each patient. As expected, with the Schnider model, the median kE_0 for children was higher compared with adults. This result is consistent with Jeleazcov results: the equilibration rate constant kE_0 is age-dependent and decreases with increasing age.⁶

Finally, after this pharmacodynamic approach, we calculated the pharmacokinetic performances of the Kataria and Schnider models using propofol dosages performed on blood samples drawn at equilibrium. Unlike the pharmacodynamic performances, our results demonstrated a moderate performance for both pharmacokinetic models to predict plasma propofol concentrations.

These findings contrast with the good pharmacodynamic performances calculated in the first part of the study and suggest that PK-PD approach improves global modeling of propofol administration to reach a given depth of anesthesia in children. In addition, clinical pharmacodynamic feedback, such as BIS, seems to be a useful tool to blunt interindividual variability, which is particularly pronounced in pediatric population.⁷

There are some potential limitations to this study. The first is the influence of remifentanyl on the accuracy of propofol concentrations. A decrease of the central volume of distribution and distributional clearance of remifentanyl was induced by coadministration of propofol; however, remifentanyl did not seem to alter the pharmacokinetics of propofol.³² Furthermore, in our study, all blood samples for propofol dosage were drawn at least 15 min after the discontinuation of remifentanyl infusion; given that the half-life of remifentanyl is 4 min,³³ it is unlikely that this agent has affected the predicted or measured concentrations of propofol. To investigate possible influences on the accuracy estimation, we have plotted the bias calculated with both models *versus* the total amount of remifentanyl, the total amount of propofol, the age of our prepubertal subjects, and the propofol target concentrations. Indeed, we have shown that only target propofol concentrations significantly influenced the accuracy of both models, and there was an increasing bias with increasing target concentrations.

The propofol cerebral drug effect was measured by using BIS, as applied in various previous studies.²⁰ This is the second limitation of our work. The BIS gives partial pharmacodynamic feedback limited to cortical electroencephalographic effects, whereas the anesthetics influenced both cortical and subcortical structures. Moreover, this influence

might be different according to the cortical or subcortical target, leading to different modulations of cortical or subcortical processes (e.g., loss of consciousness or response to noxious stimulus).³⁴ Thus, our results should be regarded as limited to the cortical effect of propofol.

When analyzing the raw data, a certain delay in the BIS behavior is sometimes observed. This delay may reflect the combination of the averaging algorithm to calculate the BIS and the delay in adaptation of one of the artifact-rejection processing steps. To take these delays into consideration, we included a BIS delay or lag time into our modeling work. Under accurate signal quality conditions, the average delay can in theory be estimated to be of 10 or 15 s. Some authors found a typical BIS delay of around 20 s when applying the model with estimated or fixed E_{\max} , which comes slightly longer than the theoretical delay.³⁵ In agreement with this latter study, we have found that a time delay of 30 s significantly decreased the NONMEM OF compared with a 0 or 15-s lag time.

The third limitation is the range of age of our prepubertal subjects, limited to 6–13 yr. In this age range, however, propofol seems to be particularly relevant given, on the one hand, the possibility of placement of an intravenous line in good conditions and, on the other hand, the potential benefits in terms of recovery.

Conclusion

In prepubertal children, the predicted concentration/effect relationship was best described using the Schnider model initially described for adults, whereas the classic pediatric models were less efficient. This unexpected finding may be explained by the integration, in the Schnider model, of significant covariates relating to clearance calculations that seem relevant in our pediatric population. In addition, the introduction of a covariate “pubertal status” improved the pharmacodynamic model linked to the Schnider pharmacokinetic set in a population of children and young adults. Calculation of pharmacodynamic parameters revealed shorter T_{peak} and higher Ce_{50} in children compared with adults. Our study suggested that the Schnider model might be useful for TCI of propofol in children older than 6 yr. However, this assumption should be investigated by further clinical studies.

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