An Evaluation of Using Population Pharmacokinetic Models to Estimate Pharmacodynamic Parameters for Propofol and Bispectral Index in Children

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ABSTRACT

Background: To study propofol pharmacodynamics in a clinical setting a pharmacokinetic model must be used to predict drug plasma concentrations. Some investigators use a population pharmacokinetic model from existing literature and minimize the pharmacodynamic objective function. The purpose of the study was to determine whether this method selects the best-performing pharmacokinetic model in a set and provides accurate estimates of pharmacodynamic parameters in models for bispectral index in children after propofol administration.

Methods: Twenty-eight children classified as American Society of Anesthesiologists physical status 1 who were given general anesthesia for dental treatment were studied. Anesthesia was given using target-controlled infusion of propofol based on the Kataria model. Propofol target plasma concentration was 7 μg/ml for 15 min, followed by 1 μg/ml for 15 min or until signs of awakening, followed by 5 μg/ml for 15 min. Venous blood samples were taken 1, 2, 5, 10, and 15 min after each change in target. A classic pharmacokinetic-pharmacodynamic model was estimated, and the methodology of other studies was duplicated using pharmacokinetic models from the literature and (re-)estimating the pharmacodynamic models.

Results: There is no clear relationship between pharmacokinetic precision and the pharmacodynamic objective function. Low pharmacodynamic objective function values are not associated with accurate estimation of the pharmacodynamic parameters when the pharmacokinetic model is taken from other sources.

Conclusion: Minimization of the pharmacodynamic objective function does not select the most accurate pharmacokinetic model. Using population pharmacokinetic models from the literature instead of the 'true' pharmacokinetic model can lead to better predictions of bispectral index while incorrectly estimating the pharmacodynamic parameters.

What We Already Know about This Topic

- Replacing individual with population pharmacokinetic models from the literature for pharmacodynamic modeling has not been validated

What This Article Tells Us That Is New

- Using population pharmacokinetic models from the literature to predict plasma propofol concentrations in 28 children did not provide accurate estimates of pharmacodynamic parameters

PROPOFOL is widely used to manage the hypnotic component of anesthesia in children because of its beneficial pharmacologic characteristics, although caution is warranted in relation to side effects such as the propofol

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infusion syndrome.[1] Pharmacokinetic-pharmacodynamic (PK-PD) models predicting the time course of drug concentration and effect might be helpful to optimize drug administration if found to be an accurate prediction of reality. A number of population pharmacokinetic models have been developed to predict propofol plasma concentrations in children for arterial blood samples,[2–4] venous blood samples,[5–7] or both.[8] In two recent studies, Rigouzzo *et al.*[9,10] suggested that a propofol model describing the PK-PD relationship in adults[11,12] might be used in children.

Some of these population pharmacokinetic models are used in target-controlled infusion (TCI) regimens to modulate predicted propofol plasma concentrations. However, plasma concentrations are only of secondary importance in anesthesia because plasma is not the site of drug effect. For propofol anesthesia, cerebral drug effects can be measured and are quantal (*e.g.*, loss and return of consciousness, tolerance to noxious stimulus) or continuous (*e.g.*, electroencephalographic data) in nature. The Bispectral Index (BIS, Covidien, Norwood, IL), a quantitative parameter derived from the frontal electroencephalogram, has been validated as a measure of propofol cerebral drug effect in children older than 1 yr.[9,10,13,14]

To study propofol pharmacodynamics in a clinical setting, where dosing varies according to patient requirements, a pharmacokinetic model must be used to predict drug plasma concentrations. The methodologically best approach is the classic PK-PD approach in which population and individualized pharmacokinetic models are estimated using blood samples drawn from the study patients and the individualized pharmacokinetic model used for subsequent pharmacodynamic estimation. However, drawing blood samples is not always practical or possible in some clinical situations. Some investigators have instead applied what we describe in this investigation as the PK(predicted)-PD approach, where the individualized pharmacokinetic model is replaced by a population pharmacokinetic model obtained from existing literature. This fixed population model is then used to produce the pharmacokinetic predictions necessary to study the pharmacodynamics. In this investigation, to clarify the particular pharmacokinetic model used, the word "predicted" can be changed to indicate the origin of the pharmacokinetic model. For example, a PK-(Kataria)-PD model indicates that the Kataria model[6] was used for pharmacokinetic predictions.

The PK(predicted)-PD approach leads to questions about the accuracy of the population predictions for individuals in a particular clinical situation. One approach is to simply take the accuracy for granted.[15] This seems difficult to justify because a number of pharmacokinetic models are available in the literature, each giving different predictions for a given situation. Another approach is to consider a number of pharmacokinetic models and choose the best one based on some quality of the corresponding pharmacodynamic estimation, such as the objective function.[10,16] This approach assumes that the best- performing pharmacokinetic model can be identified by the lowest objective function from the corresponding pharmacodynamic estimation. However, this relationship has not yet been experimentally demonstrated. Studies using this approach also estimate important pharmacodynamic model parameters, such as effect-site equilibration constant (k_{e0}) or the effect-site concentration for 50% effect (Ce_{50}), by minimization of the pharmacodynamic objective function. However, there is no evidence that low values for the objective function are associated with accurate estimation of these parameters when the pharmacokinetic model is taken from other sources. It has been recently shown that fundamental flaws can be introduced when applying predicted instead of measured propofol plasma concentration when investigating the half-life for the effect-site equilibration in adults.[17–19]

The purpose of the current study was to test two hypotheses: that the PK(predicted)-PD approach selects the best-performing pharmacokinetic model from those considered, and that the PK(predicted)-PD approach provides accurate estimates of pharmacodynamic model parameters. We performed propofol TCI-driven anesthesia on children and obtained propofol plasma concentrations from blood samples and BIS values as a measure of cerebral drug effect. From these data we estimated a classic PK-PD model, where both a pharmacokinetic and pharmacodynamic model are estimated. We also duplicated the methodology of other studies by estimating PK(predicted)-PD models, *i.e.*, using pharmacokinetic models from the literature and (re-)estimating only the pharmacodynamic models. By comparing the estimation results of the different approaches we determined the ability of the PK(predicted)-PD approach to identify the best-performing pharmacokinetic model and provide informative estimates for the true pharmacodynamic parameters.

Materials and Methods

Clinical Protocol

After Ethics Committee approval (Ghent University Hospital, Gent, Belgium), clinical trial registration (EUDRACT 2005-001797-27), written informed consent of the parents or legal representative obtained by the dentist, and a clinical examination done by the anesthesiologist, 28 children classified as American Society of Anesthesiologists physical status 1 were enrolled in the study. Patients were divided in four groups according to age: 7 children in group 1 age 3–5 yr, 7 children age 5–7 yr in group 2, 7 children age 7–9 yr in group 3, and 7 children age 9–11 yr in the fourth group. All children were scheduled for dental treatment under general anesthesia. Exclusion criteria were allergy to any of the constituents of propofol or local anesthetics, previous adverse anesthetic experience, evidence of major preexisting disease, suspected difficult airway, concomitant disease, or antibiotic treatment. No premedication was offered to the patients. The skin was locally anesthetized by applying eutectic mixture of local anesthetic cream (EMLA, AstraZeneca, Ukkel, Belgium) over the site of the peripheral veins 1 h before the procedure.

Noninvasive monitoring (heart rate, noninvasive blood pressure monitoring, saturation, end-tidal carbon dioxide) was established before induction of anesthesia. The propofol cerebral drug effect was continuously monitored using the bispectral index (BIS). BIS (version 4.0, XP) was derived from the frontal electroencephalogram and calculated by the A-2000 BIS Monitor® (Covidien, Newton, MA) using three BIS-Sensor electrodes (pediatric size) or the four-sensor electrode, depending on the patient's age. The BIS value ranges from 100 to 0. The smoothing time of the BIS monitor was set to 15 s.

Venous access was established with two 20- or 22-gauge peripheral intravenous cannulae. The first cannula was connected to the infusion pump, and the second cannula was used for blood sampling. The TCI system used to control the propofol infusion comprised a syringe infusion pump (Asena, Carefusion, Basingstoke, United Kingdom) controlled by a computer programmed with RUGLOOPII (Demed, Temse, Belgium) using a pharmacokinetic model for propofol administration in children, in a study previously published by Kataria *et al.*[6] Propofol was started at a target plasma concentration of 7 μg/ml for 15 min, followed by a target concentration of 1 μg/ml for another 15 min or until signs of awakening (BIS more then 80, movement, eye opening). Finally, the infusion was followed by a target plasma concentration of 5 μg/ml for 15 min. After initial loss of consciousness a laryngeal mask was inserted. No opioid was administered. All children received a crystalloid infusion of 4–5 ml/kg/h during the study. Each blood sample (2 ml per sample) was replaced by 2 ml of crystalloid solution. During the procedure the children were kept warm with a Bair Hugger (Arizant Healthcare, Eden Prairie, MN). The complete study was executed before the start of surgery.

Venous blood samples were collected at baseline (upon placement of the cannula) and after 1, 2, 5, 10, and 15 min at a target of 7 μg/ml. After decreasing the target concentration to 1 μg/ml, blood was withdrawn after 1, 2, 5, 10, and 15 min when possible. After increasing the target concentration to 5 μg/ml, blood samples were obtained at 1, 2, 5, 10, and 15 min. At that time the study period was completed and the anesthesia was continued at the discretion of the anesthesiologist in charge. The collected blood samples (EDTA) of each child were centrifuged, and the obtained plasma was stored in a refrigerator at a temperature at −80°C for further analyses. Propofol (bound and free) plasma concentrations were analyzed using a validated liquid chromatographic fluorescence detection method. In short, plasma (500 μl) was treated with 1 ml acetonitrile (containing the internal standard 2,4-di-tert-butylfenol) to initiate plasma protein precipitation. After centrifugation, 10 μl of the clear supernatant is injected into the liquid chromatography system (Kontron 325 pump system, Kontron Instruments, Milano, Italy) and Hitachi AS2000A autosampler (Hitachi, Tokyo, Japan). Separation was obtained on a Discovery C18 column (5 μm, 50 × 2.1 mm; Supelco, Sigma-Aldrich, Bornem, Belgium) using a water/acetonitrile gradient. Detection was achieved using a Shimadzu RF-10AXL fluorescence detector (Shimadzu, Kyoto, Japan) (λ_{ex} 276 and λ_{em} 310 nm). Validation (according to Food and Drug Administration guidelines: Bioanalytical Method Validation, Guidance for Industry) data include: limit of detection 0.0935 μg/ml; limit of quantification 0.2 μg/ml, weighted (1/x) linear regression model calibration curves from 0.20 to 15.0 μg/ml (11 calibrators + blank), $R^2 = 0.9961$ (n = 6). Selectivity was assured on the basis of the analysis of multiple blank human plasma batches and injection of potential comedication standards. Independently prepared quality control samples (0.5, 0.75, 3.5, and 12.5 μg/ml) were used to evaluate precision (repeatability 2.55–8.37 relative SD %); (reproducibility 4.60–6.84 relative SD %, n = 6) and accuracy (−7.59 to −3.39 bias % relative error), and later to accept individual sample runs.

Pharmacokinetic Dynamic Model

A three-compartmental mammillary model with parameters V_1, V_2, V_3, CL, Q_2, and Q_3 was applied enlarged with an effect-site. The effect-site was assumed to be linked to the central pharmacokinetic compartment with a first-order equilibrium constant of k_{e0}. A classic sigmoidal maximal possible drug effect model (E_{max}) was used to describe the relationship between propofol effect-site concentration (*Ce*) and the BIS as a measure of propofol cerebral drug effect:

$$\text{Effect} = E_0 + (E_{max} - E_0)\frac{Ce^{\gamma}}{Ce_{50}^{\gamma} + Ce^{\gamma}}$$

where Effect is the measured BIS value, E_0 is the baseline measurement when no drug is present, E_{max} is the maximal possible drug effect, *Ce* is the calculated propofol effect-site concentration, Ce_{50} is the *Ce* associated with 50% maximal drug effect, and γ is the steepness of the concentration-*versus*-response relation. The delay in the reported BIS index was assumed to be 10 s as published previously.[17] For the current study E_{max} was fixed to 0 and E_0 to 95.

Unless otherwise stated, interindividual variability was assumed to be log-normally distributed:

$$\theta_i = \theta_{TV} \cdot e^{\eta_i}$$

where θ_i is the parameter value in the *i*th patient, θ_{TV} is the typical value of the parameter in the population, and η_i is a random variable in the *i*th patient with a mean of 0 and a variance of ω^2. Interindividual 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 intraindividual variability for the observed propofol central compartment concentration was modeled using constant coefficient of variance model, and for BIS index this was modeled using an additive error model. Model estimation was performed using NONMEM VI 2.0 (ICON, Dublin, Ireland).

Classic PK-PD Approach. The sequential method[20,21] was used. More specifically, a population pharmacokinetic model was estimated using patients' individual measured

Table 1. Propofol Pharmacokinetic Models from the Literature

PK Model	Parameters
Kataria[7]	V_1 = 0.41 * WGT V_2 = 0.78 * WGT + 3.1 * AGE − 16 V_3 = 6.9 * WGT CL = 0.035 * WGT Q_2 = 0.077 * WGT Q_3 = 0.026 * WGT
Paedfusor[2,29]	V_1 = 0.4584 * WGT K_{10} = 0.1527 * $WGT^{-0.3}$ K_{12} = 0.114 K_{21} = 0.055 K_{13} = 0.0419 K_{31} = 0.0033
Marsh[5]	V_1 = 0.343 * WGT K_{10} = 0.1 K_{12} = 0.0855 K_{21} = 0.033 K_{13} = 0.021 K_{31} = 0.0033
Short[8]	V_1 = 0.432 * WGT K_{10} = 0.0967 K_{12} = 0.1413 K_{21} = 0.1092 K^{13} = 0.0392 K_{31} = 0.0049
Rigby-Jones[3]	V_1 = 0.584 * WGT V_2 = 1.36 * WGT V_3 = 5.67 * WGT + 103 CL = 0.0302 * WGT Q_2 = 0.0160 * WGT Q_3 = 0.0133 * WGT
Rigby-Jones (multicenter)[1]	V_1 = 7.76 * PWT V_2 = 14.4 * PWT V_3 = 83.9 * PWT CL = 0.614 * $PWT^{0.75}$ Q_2 = 0.839 * $PWT^{0.75}$ Q_3 = 0.252 * $PWT^{0.75}$ PWT = WGT/15
Schuttler[9]	V_1 = 9.3 * $PWT^{0.71}$ * $(AGE/30)^{-0.39}$ * (1 + BOL * 1.61) V_2 = 44.2 * $PWT^{0.61}$ * (1 + BOL * 0.73) V_3 = 266 CL = 1.44 * $PWT^{0.75}$ Q_2 = 2.25 * $PWT^{0.62}$ * (1 − VEN * 0.40) * (1 + BOL * 2.02) Q_3 = 0.92 * $PWT^{0.55}$ * (1 + BOL * − 0.48) PWT = WGT/70 VEN = 1 (venous samples) BOL = 0 (infusion dosing, not bolus)
ShangGuan[4]	V_1 = 7.41 * PWT V_2 = 54.6 * PWT V_3 = 7.2 * PWT CL = 0.185 * $PWT^{0.75}$ Q_2 = 0.614 * $PWT^{0.75}$ Q_3 = 0.692 * $PWT^{0.75}$ PWT = WGT/13.7
Schnider[13,14]	V_1 = 4.27 V_2 = 18.9 − 0.391 * (AGE − 53) V_3 = 238 CL = 1.89 + 0.0456 * (WGT - 77) − 0.0681 * (LBM - 59) + 0.0264 * (HGT - 177) Q_2 = 1.29 − 0.024 * (AGE - 53) Q_3 = 0.836 LBM_{male} = 1.1 * WGT - 128 * (WGT/HGT)2 LBM_{female} = 1.07 * WGT - 148 * $(WGT/HGT)^2$

* Covariate terms used are subject weight (WGT) in kilograms, subject age (AGE) in years, and subject height (HGT) in centimeters. BOL = bolus; CL = clearance; LBM = lean body mass; PK = pharmacokinetic; PWT = population median weight; VEN = venous.

blood samples first, producing a population pharmacokinetic model and individual (*post hoc*) pharmacokinetic estimates. In the second stage, the pharmacodynamic model population parameters are estimated with the individual pharmacokinetic model parameters fixed to their *post hoc* estimates.

PK(Predicted)-PD Approach. In this approach, the patient pharmacokinetic model is fixed to one of the previously published population pharmacokinetic models; these are shown in table 1. No pharmacokinetic estimation is performed because the time course of the propofol plasma concentration is calculated from the fixed pharmacokinetic model, the patient covariates in the model, and the given propofol dose per time. The pharmacodynamic model is estimated with a population approach using the patient's individual BIS data.

Indices for Assessment

For all pharmacokinetic models, goodness-of-fit plots were constructed for each data set using each model. The plots depict the predicted concentrations *versus* the observed concentrations of propofol. In addition, the predictive performances of the pharmacokinetic models were analyzed using prediction error analysis, as described by Varvel *et al.*[22]

Prediction error (PE) for plasma concentrations was calculated using the following equation:

$$\mathrm{PE} = \frac{C_{\mathrm{plasma}}\ \mathrm{observed} - C_{\mathrm{plasma}}\ \mathrm{predicted}}{C_{\mathrm{plasma}}\ \mathrm{predicted}} \times 100$$

Prediction error for BIS values was calculated using the following equation:

$$\mathrm{PE} = \mathrm{BIS\ observed} - \mathrm{BIS\ predicted}$$

PE is an indication of the bias of the achieved concentrations, and the absolute value of the PE (|PE|) is a measure of the precision.

For each individual, median prediction error (MDPE) and median absolute prediction error (MDAPE) were calculated as measures of the accuracy and precision of the Cplasma prediction. In the *i*th subject:

$$\text{MDPE}_i = \text{median}\{\text{PE}_{ij},\ j = 1, \ldots, N_i\}$$

where N_i is the number of PE values obtained for the *i*th subject. Hereby, an MDPE value of 0 means no bias.

MDAPE indicates the precision of the C_{plasma} prediction. In the *i*th subject:

$$\text{MDAPE}_i = \text{median}\{|\text{PE}_{ij}|, j = 1, \ldots, N_i\}$$

where N_i is the number of PE values obtained for the *i*th subject. The closer to 0, the more precise is the model.

To reflect the quality of the pharmacodynamic model and predictions the NONMEM objective function value was used. All of the objective function value comparisons concern estimation of the pharmacodynamic model using the BIS pharmacodynamic observations from the current study in conjunction with a fixed pharmacokinetic model, so the comparisons are valid.

Results

Data from all included 28 patients were used in the analysis. In total, 443 venous blood samples were obtained and used for the analysis. In 5 patients, 1 blood sample was missing due to technical reasons (1-min sample at plasma concentration [Cp] 1 in patient 1, 1-min sample at Cp7 in patient 9, 15-min sample at Cp1 in patient 11, 1-min sample at Cp7 in patient 18, 1-min sample at Cp1 in patient 21). Nineteen boys and nine girls were included. Their demographics were (median [min–max]) age, 6.5 y (range, 4–11 y); weight, 21.5 kg (range, 18–54 kg); height, 119 cm (range, 105–152 cm). All NONMEM runs successfully completed the covariance step and reported a condition number less than 1,000.

Classic PK-PD Approach

For the classic PK-PD approach, a three-compartment model fit the data. The typical values, intraindividual and residual variability for the estimated population model, are shown in table 2. The interindividual variance (ω) values for V_2, V_3, and Q_2 were fixed to 0 to obtain a stable estimation. For all patients, the observed, population-predicted, and *post hoc* predicted plasma concentrations are shown in figure 1. The observed/population predicted and observed/*post hoc* predicted plasma concentrations *versus* time and *versus* observed plasma concentrations graphs are shown in figure 1. Except for some rather high plasma concentrations, an overall accurate fit was found as indicated by the smoothed curves. This is reflected by the population and *post hoc* median (absolute) prediction errors as shown in table 3.

Table 2. Pharmacokinetic Model Estimated from the Plasma Concentration Observations from the Current Study

Parameter	Units	Typical Value	Relative SD
V_1	l/kg	0.174	84%
V_2	l/kg	0.234	0 fixed
V_3	l/kg	0.951	0 fixed
CL	$l \cdot min^{-1} \cdot kg^{-1}$	0.0393	15.2%
Q_2	$l \cdot min^{-1} \cdot kg^{-1}$	0.102	0 fixed
Q_3	$l \cdot min^{-1} \cdot kg^{-1}$	0.0333	24.7%
Residual SD	%	18.4	

From the classic pharmacokinetic-pharmacodynamic approach. CL = clearance.

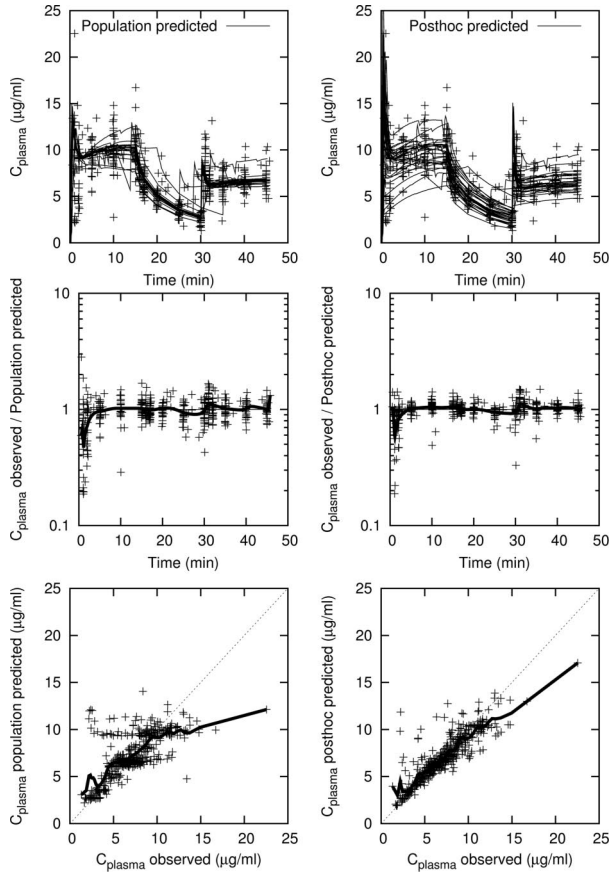

Fig. 1. From the classic pharmacokinetic-pharmacodynamic approach, pharmacokinetic population and *post hoc* predictions for the current study *versus* observed propofol plasma concentrations and time. Observations are marked as (+).

Sequentially, a sigmoid E_{max} model was used to describe the pharmacodynamic relationship between concentration and cerebral effect as measured by BIS.

For the pharmacodynamic model, the typical values and standard errors for k_{e0} and effect-site concentration Ce_{50} and the NONMEM objective function for the pharmacodynamic model are shown in table 3. Figure 2 shows the observed, population-predicted, and *post hoc* predicted BIS values for all patients. An overall observed *versus* predicted analysis revealed an acceptable pharmacodynamic model prediction (fig. 2). We did not find any statistically signifi-

Table 3. Pharmacokinetic Predictive Performance and Results from PD Model Estimation

	PK Performance		PD Estimation				
PK Model	MDPE (%)	MDAPE (%)	Objective Function	k_{e0} (l/min)	Ce_{50} (μg/ml)	γ	SD(res)
Post hoc	0.8	8.6	77385.25	0.79	3.85	1.50	7.9
Population	−0.6	14.0					
Asymptotic standard error				0.12	0.11	0.06	2.2

From the classic pharmacokinetic-pharmacodynamic approach.

Ce_{50} = effect-site concentration for 50% effect; k_{e0} = effect-site equilibration constant; γ = steepness of the concentration-*versus*-response relation; MD(A)PE = median (absolute) performance error; PD = pharmacodynamic; PK = pharmacokinetic; SD(res) = residual standard deviation.

cant relationship ($P < 0.05$) between patient age, height, or sex on the estimated pharmacokinetic or pharmacodynamic model parameters.

PK(Predicted)-PD Approach

For the PK(predicted)-PD approach, the pharmacokinetic predictions are obtained from the fixed models described in table 1. For these applied pharmacokinetic models, figure 3 shows the relationship between predicted *versus* observed propofol plasma concentrations and also depicts the ratio between predicted/observed propofol plasma concentration *versus* time. The predictive performance of the applied pharmacokinetic models is shown in table 4. The Marsh model shows the best and the Schnider model the worst pharmacokinetic performance as measured by MDPE and MDAPE. We did not see any advantage of pharmacokinetic models developed with venous samples to predict our (venous) samples. This suggests arterial *versus* venous sampling is dominated by other sources of variation. Differences in assay handling[23] between studies and the distinction between blood and plasma drug concentrations[24] may also influence model performance.

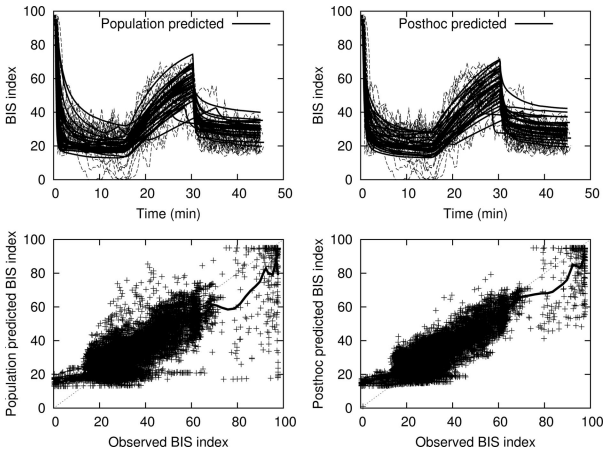

Fig. 2. From the classic pharmacokinetic-pharmacodynamic approach, pharmacodynamic population and *post hoc* predictions for the current study *versus* observed Bispectral Index (BIS) and time. Observations are marked as (+) or as (smoothed) dotted line.

A sigmoid E_{max} model was used to describe the pharmacodynamic relationship between concentration and cerebral effect as measured by BIS. The typical values for k_{e0} and effect-site concentration Ce_{50} and the NONMEM objective function for the pharmacodynamic model are shown in table 4. The PK(Schnider)-PD model gave the best pharmacodynamic fit, and the PK(Rigby-Jones)-PD model gave the worst pharmacodynamic fit as indicated by the NONMEM objective function values.

This PK(predicted)-PD approach assumes that the best-performing pharmacokinetic model can be identified by the lowest objective function from the corresponding pharmacodynamic estimation. Figure 4 shows these relationships for the data from the current study. There does not seem to be a clear relationship between MDPE or MDAPE with the objective function from pharmacodynamic estimation. Thus, it should not be assumed that this approach selects the best-performing pharmacokinetic model. In fact, in our study, it selected the worst- performing pharmacokinetic model. Alternatively, one could rank the models based on root mean squared error of the predictions; this can be seen as the SD of the residuals (SD[res]) in table 4. In this case the ranking of models is identical to that from objective function value, and the findings are same. Yet another ranking could be based on the MDAPE of the predictions, also shown in table 4. In this case the ranking of models is nearly identical, and the findings the same.

Studies using the PK(predicted)-PD approach also estimate pharmacodynamic parameters k_{e0}, Ce_{50}, and γ, by minimization of the pharmacodynamic objective function. However, there is no evidence that low objective function values are associated with accurate estimation of these pharmacodynamic parameters when the pharmacokinetic model is taken from other sources. Figure 5 shows the relationship between objective function from the PK(predicted)-PD approach and its ability to estimate the "true" pharmacodynamic parameters estimated by the classic PK-PD approach, which are marked by crosshairs. It seems that for the PK(predicted)-PD approach, *i.e.*, using a population pharmacokinetic model taken from other sources, that minimization of the pharmacodynamic objective function does not necessar-

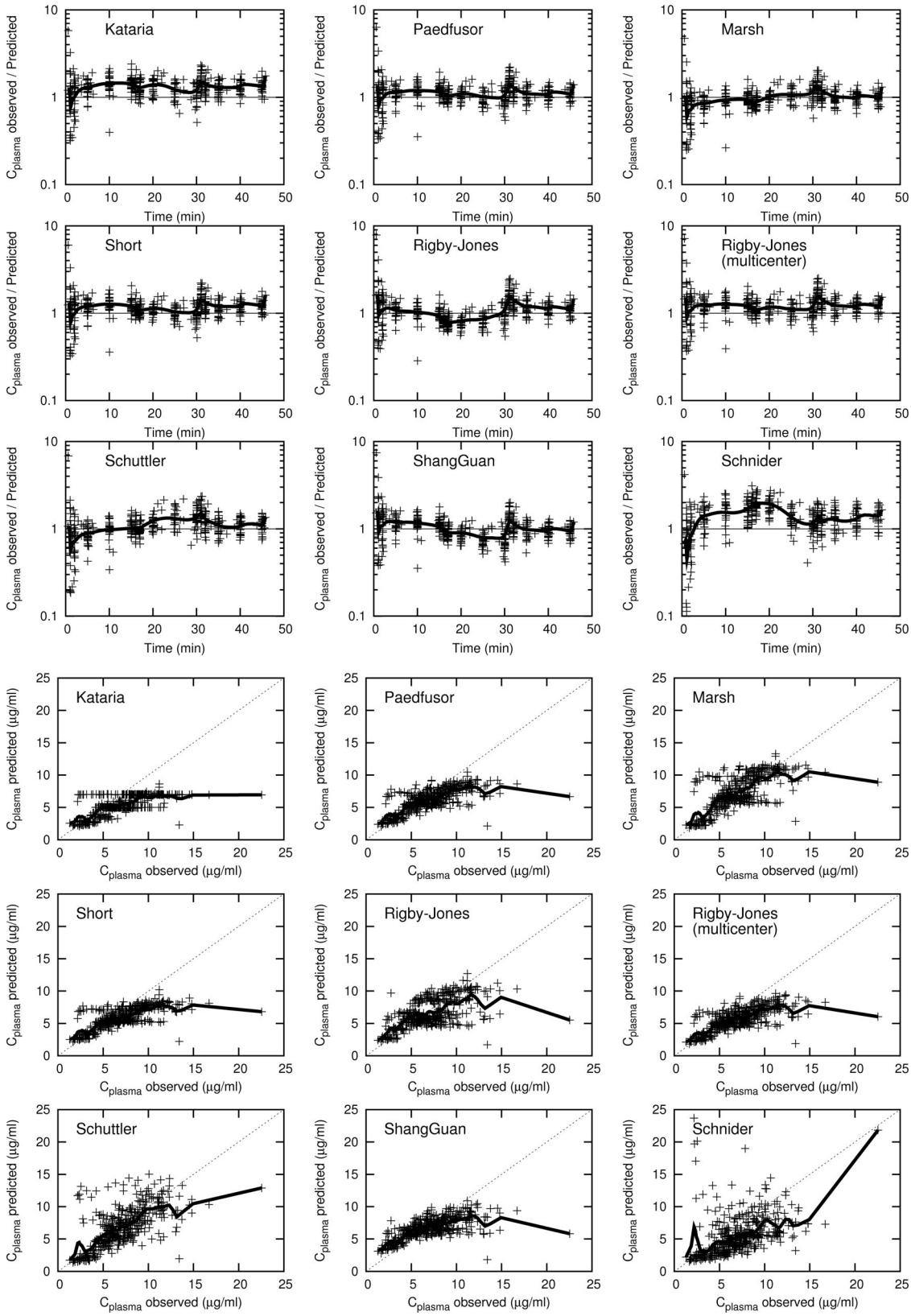

Fig. 3. From the pharmacokinetic(predicted)-pharmacodynamic approach, predicted *versus* observed graphs for propofol plasma concentrations for the pharmacokinetic(predicted) models described in table 1.

Table 4. Pharmacokinetic Predictive Performance and Results from Pharmacodynamic Model Estimation

Pharmacokinetic Model	Pharmacokinetic Performance		Pharmacodynamic Estimation					
	MDPE (%)	MDAPE (%)	Objective Function	k_{e0} (l/min)	Ce_{50} (μg/ml)	γ	SD (res)	MDAPE (BIS)
Kataria	31.3	34.1	75619.64	0.89	2.98	1.53	7.5	5.26
Paedfusor	10.4	19.0	75334.11	1.38	3.53	1.53	7.4	5.17
Marsh	−1.3	15.9	76976.42	0.93	3.33	1.12	7.8	5.50
Short	17.0	23.1	76206.88	1.24	3.41	1.58	7.6	5.50
Rigby-Jones	4.4	21.6	80904.49	2.64	3.61	1.33	8.9	6.86
Rigby-Jones Multicenter	20.9	25.8	76001.34	1.47	3.18	1.47	7.6	5.36
Schuttler	10.2	21.8	77214.12	0.72	2.78	1.02	7.9	5.48
ShangGuan	−1.0	20.7	74351.15	3.30	4.52	2.07	7.2	4.96
Schnider	41.4	46.9	74334.83	0.33	2.80	1.58	7.1	4.85

From the pharmacokinetic(predicted)-pharmacodynamic approach.

BIS = bispectral index; Ce_{50} = effect-site concentration for 50% effect; k_{e0} = effect-site equilibration constant; γ = steepness of the concentration-*versus*-response relation; MD(A)PE = median (absolute) performance error; SD(res) = residual standard deviation.

ily result in accurate estimates of the pharmacodynamic parameters.

Discussion

We found that the classic PK-PD approach results in an accurate pharmacokinetic model as evidenced by low values for MDPE and MDAPE. Surprisingly, using a population pharmacokinetic model from another source, *i.e.*, the PK(predicted)-PD approach, can lead to lower pharmacodynamic objective function values than the classic approach, but offers no guarantee of an accurate pharmacokinetic model. Interestingly, the best pharmacodynamic fit was obtained using the PK(Schnider)-PD model, while at the same time this model produced the worst pharmacokinetic predictions. We found that the PK(predicted)-PD approach does not select the best-performing pharmacokinetic model.

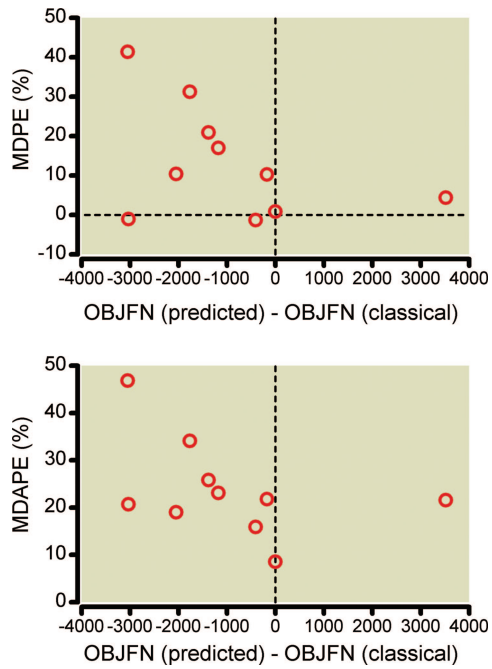

Fig. 4. For the pharmacokinetic(predicted)-pharmacodynamic approach, the relationship between objective function (OBJFN) and median (and absolute) prediction error (MD(A)PE) for the pharmacokinetic models as described in table 1. The point from the classic pharmacokinetic-pharmacodynamic approach is also included. There is no clear relationship between pharmacokinetic precision and the pharmacodynamic objective function.

Shafer *et al.* stated that the final validation of a model for TCI should be to apply it in a TCI setting and to measure the plasma concentration.[25] These validations have been performed for adults,[11,12] but not for children. Our study is a validation of the previously applied[15] Kataria model[6] for propofol plasma- controlled, TCI-driven anesthesia on children. Similar to other models,[10] we found that the Kataria pharmacokinetic model was biased and inaccurate, evidenced by poor MDPE and MDAPE. The Marsh and ShangGuan models showed low pharmacokinetic bias (MDPE) and the Marsh model the best precision (MDAPE). We also considered the Schnider model, despite its derivation from an adult population, because a recent publication suggested it may provide acceptable PK-PD performance in children.[26] However, in our study it showed pharmacokinetic bias and was inaccurate. Our results are in agreement with others,[10] who found an MDPE and MDAPE for the Schnider model of 44.3% and 44.3% and for the Kataria model of 52.2% and 52.5%, respectively. For the Paedfusor model, Absalom *et al.*[2] found lower values for MDPE (4.1%) and MDAPE (9.7%) compared with our studies. This might be because of the difference between arterial and venous blood sampling in their study and ours, respectively. The pharmacokinetic accuracy for the Short model are worse than expected, possibly because this model was developed in Chinese children, who may have altered kinetics compared with the European children used in our study.[7] On the other hand, the ShangGuan pharmacokinetic model developed in

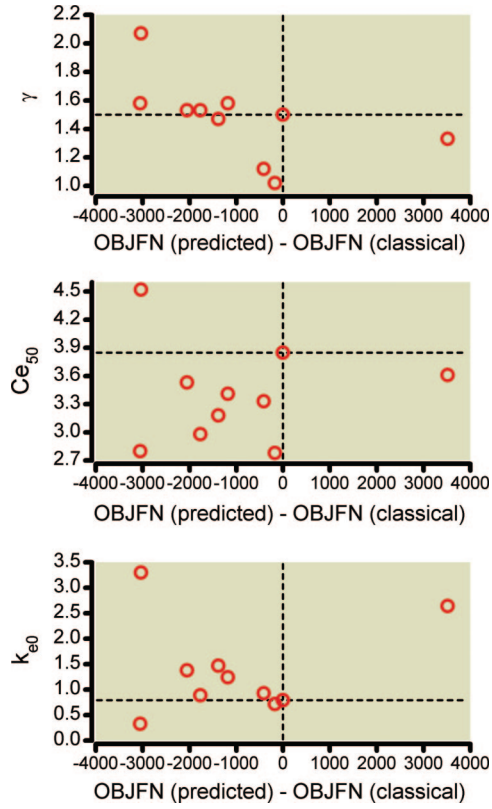

Fig. 5. For the pharmacokinetic(predicted)-pharmacodynamic approach, the relationship between objective function (OBJFN) and the estimation of pharmacodynamic parameters compared to the "true" pharmacodynamic parameters estimated by the classic pharmacokinetic-pharmacodynamic approach (indicated by *crosshairs*). Low pharmacodynamic objective function values are not associated with accurate estimation of the pharmacodynamic parameters when the pharmacokinetic model is taken from other sources.

Chinese children was nearly unbiased and showed reasonable precision.

We were able to develop a three-compartmental model from the pharmacokinetic data scaled to total body weight. It showed unbiased population and *post hoc* individual predictions with an acceptable accuracy.[27] The difficulties we experienced in estimating the population variances for V_2, V_3, and Q_2 may be related to the fact that the pharmacokinetic observations were made during TCI-driven anesthesia. TCI dosing has been mathematically proven to have lower inter-individual variability compared with bolus dosing.[28] This reduced uncertainty in plasma propofol observations across the population makes the data less informative for estimation of a population pharmacokinetic model, thereby making the previously mentioned simplifications to the model structure necessary.

The pharmacokinetics and dynamics of a drug should be modeled within the same patient group to obtain an unbiased description of the dose-response relationship of a drug,[29] and the classic PK-PD approach is methodologically the best estimate of the "true" PK-PD model. In the current study we found a Ce_{50} of 3.85 μg/ml, a value similar to the "measured" Ce_{50} of 4.03 μg/ml found by Rigouzzo *et al.*[9] Rigouzzo *et al.* also found a "target" Ce_{50} using the Kataria pharmacokinetic model to be 2.94 μg/ml, which can be compared with that from our PK(Kataria)-PD model, 2.98 μg/ml. In a different study,[10] the same authors found a Ce_{50} of 2.64 μg/ml when the Schnider pharmacokinetic model was used. This value can be compared with that of our PK-(Schnider)-PD model, where a Ce_{50} of 2.80 μg/ml was found. It seems that the underprediction of the Kataria and Schnider pharmacokinetic models leads to too-low estimates of Ce_{50}. There does not seem to be any relationship indicating any particular Ce_{50} value. This suggests that the PK(predicted)-PD approach does not accurately estimate the true value of Ce_{50}. The same must also apply to covariate relationships with Ce_{50}, although this is claimed in other studies.[16]

A wide variability of k_{e0} values between the PK(predicted)-PD models is demonstrated, clearly illustrating the influence of the applied pharmacokinetic model on the estimated value of k_{e0}. There does not seem to be any relationship indicating any particular k_{e0} value. This suggests that the PK(predicted)-PD approach does not accurately estimate the true value of k_{e0}. We used a 10-s BIS delay in our calculations, which will influence the absolute value of k_{e0}, a previously described approach.[17] Similar to other studies,[19] we fixed the BIS values for E_0 and E_{max} to 0 and 95, respectively, although in other studies these values have been estimated.[16]

One may be tempted to argue that the limitations of the pharmacokinetic estimation may degrade the estimation of the true pharmacodynamic parameters, and thus the inability of the PK(predicted)-PD models to find the same values as the classic PK-PD approach, does not necessarily mean that the PK(predicted)-PD approach did not find the true pharmacodynamic parameters. However, it should be noted that for the PK(predicted)-PD models considered, there is no clear relationship between model fit (objective function or residual error) and any particular estimated pharmacodynamic parameter value. For example, the best two PK(predicted)-PD models estimate very different values for all of the pharmacodynamic parameters. Because the PK(predicted)-PD approach fails to indicate any particular pharmacodynamic value, it must also have failed at indicating the true pharmacodynamic parameter.

It was an unexpected result that the classic PK-PD approach did not lead to the lowest objective function from pharmacodynamic estimation because it does provide the best estimates of the true pharmacokinetic model for each individual. The reason for this is probably the shortcomings of k_{e0} and the sigmoidal E_{max} model to describe the relationship between BIS and plasma compartment concentration. BIS is a complex variable measured from the brain, a very complex organ. There may be time-dependent and/or level-dependent components to the BIS that are not properly described with the sigmoidal E_{max} model. When such pharmacodynamic model misspecification is present, some specific

pattern of misprediction of the pharmacokinetic model might lead to better pharmacodynamic predictions, by "compensating" for specific shortcomings of the pharmacodynamic model. This phenomenon may be occurring in the PK-PD models studied here. The evidence for this is that the PK(Schnider)-PD model performs quite well for predicting pharmacodynamic responses but poorly predicts the pharmacokinetic responses. Therefore, an improved pharmacodynamic model for BIS may allow the PK(predicted)-PD approach to perform better, and it also would improve the classic PK-PD approach. Another study[9] did not find pharmacodynamic model misspecification; however, only nearly steady-state conditions were considered. At the same time, other pharmacokinetic model structures, such as physiologically-based models[30] or the use of transit compartments,[31] may also help "unify" pharmacokinetic and pharmacodynamic accuracy within a single model but these need to be properly scaled for application in children.

Rigouzzo *et al.*[10] suggested that the adult Schnider model might be useful for TCI of propofol in children. Their reasoning was based on good results from the PK(Schnider)-PD approach, which they used in their study. The current study confirmed the good pharmacodynamic performance of this model but found that its pharmacokinetic accuracy in children is poor, worse than all other models tested. Therefore, one cannot argue for use of the Schnider pharmacokinetic model in children on the grounds of its pharmacokinetic accuracy. On the other hand, one could argue that for some anesthesiologic applications, pharmacokinetic accuracy is of little importance provided the pharmacodynamic accuracy is good. This approach represents a paradigm shift in the application of TCI systems where, instead of a target constant drug concentration, the target is some desired pharmacodynamic response. Drug-dosing profile is then adjusted to achieve a constant pharmacodynamic target, possibly requiring a nonconstant time course of drug concentration. The good pharmacodynamic performance of the PK(Schnider)-PD model coupled with its poor pharmacokinetic accuracy gives us a hint that these drug dosing profiles may exist. Of course, the Schnider pharmacokinetic model may not be optimal for this purpose and other optimized models could be applied. Future studies may address whether this approach has any advantages to the current TCI approach in anesthesiologic applications.

We conclude that for PK-PD models of BIS in children after propofol administration using fixed pharmacokinetic models from the literature and estimating the pharmacodynamic model does not ensure good pharmacokinetic accuracy or provide informative estimates for pharmacodynamic parameters. It can, however, provide for better pharmacodynamic model fit than the classic PK-PD approach. It seems that there is some misspecification of the sigmoidal E_{max} pharmacodynamic model for BIS response in children. If the sigmoidal E_{max} pharmacodynamic model is used, then some specific pattern of misprediction of the pharmacokinetic model might lead to better pharmacodynamic predictions, by "compensating" for specific shortcomings of the pharmacodynamic model. For applications where pharmacodynamic accuracy is of primary importance these dosing profiles may prove useful.

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