Early Phase Pharmacokinetics but Not Pharmacodynamics Are Influenced by Propofol Infusion Rate

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Background: Conventional compartmental pharmacokinetic models wrongly assume instantaneous drug mixing in the central compartment, resulting in a flawed prediction of drug disposition for the first minutes, and the flaw affects pharmacodynamic modeling. This study examined the influence of the administration rate and other covariates on early phase kinetics and dynamics of propofol by using the enlarged structural pharmacokinetic model.

Methods: Fifty patients were randomly assigned to one of five groups to receive 1.2 mg/kg propofol given with the rate of 10 to 160 mg · kg^{-1} · h^{-1}. Arterial blood samples were taken frequently, especially during the first minute. The authors compared four basic pharmacokinetic models by using presystemic compartments and the time shift of dosing, LAG time. They also examined a sigmoidal maximum possible drug effect pharmacodynamic model. Patient characteristics and dose rate were obtained to test the model structure.

Results: Our final pharmacokinetic model includes two conventional compartments enlarged with a LAG time and six presystemic compartments and includes following covariates: dose rate for transit rate constant, age for LAG time, and weight for central distribution volume. However, the equilibration rate constant between central and effect compartments was not influenced by infusion rate.

Conclusions: This study found that a combined pharmacokinetic-dynamic model consisting of a two-compartmental model with a LAG time and presystemic compartments and a sigmoidal maximum possible drug effect model accurately described the early phase pharmacology of propofol during infusion rate between 10 and 160 mg · kg^{-1} · h^{-1}. The infusion rate has an influence on kinetics, but not dynamics. Age was a covariate for LAG time.

CONVENTIONAL multicompartmental mammillary pharmacokinetic models assume that drug added to the central compartment is instantaneously completely mixed and that this mixed plasma instantaneously appears in the arterial circulation. The failure of these models to accurately predict the time course of arterial drug concentration in the first minutes after administration is the result of this flawed assumption and has been extensively described.[1–6] Although a physiologically based pharmacokinetic model may be considered an accurate description of drug disposition from the start of drug administration, difficulty in collecting the extensive data for the model development and the fact that such models are not readily fitted to clinical pharmacokinetic-driven drug infusion caused by their complexity, have limited their applicability into pharmacokinetic studies.[5,7] More experimental approaches have been described to reveal the delay between drug administration and appearance of the drug at the site of arterial blood sampling. Standard lag time models (LAG model), which represent the time shift of dosing as if the drug was in fact administered at a later time, and analytical solutions of the TRANSIT compartment model (TRANSIT model), which depicts a multiple-step process represented by a chain of presystemic compartments and differs from the LAG model by the presence of one additional parameter, a transit rate constant, have been used by various authors.[8] Others have used more sophisticated recirculatory models to analyze arterial drug concentrations *versus* time using estimated cardiac output from the first pass area under the curve in animal research.[7]

A first-order process, described by k_{e0}, characterizes the drug transfer between the plasma and effect site.[9] When using a combined pharmacokinetic-dynamic model to describe the complete dose-response relationship, misspecification in the pharmacokinetic model over the first few minutes will result in a less accurate interpretation of the plasma effect-site equilibration.[6]

Induction dose, time course of drug concentration, and drug effect of propofol are dependent on administration rate. Therefore, the inclusion of dose rate into kinetic-dynamic model in the early phase might optimize the description of the time course of early drug disposition and drug effect.[6,10]

The aim of this study was to investigate if a compartmental model including LAG and TRANSIT models

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can describe the time course of arterial propofol concentration in the first minutes after administration more accurately than a classic compartmental model. We also studied the influence of the pharmacokinetic model on the description of propofol's cerebral drug effect as measured by the Bispectral Index (BIS). In addition, we aimed at investigating the influence of propofol's administration rate on these early phase kinetics and dynamics.

Materials and Methods

Clinical Protocol

After securing local ethics committee (National Defense Medical College, Saitama, Japan) approval and written informed consent, we enrolled 50 patients who were American Society of Anesthesiologists physical status I or II, aged 30–76 yr, and scheduled to undergo elective gynecologic, orthopedic, or digestive surgery. Exclusion criteria included body mass index greater than 30, neurologic disorder, recent use of psychoactive medicine, and significant heart, hepatic, or renal impairment.

All patients were randomly assigned to one of five groups to receive 1.2 mg/kg propofol (1% Diprivan®; AstraZeneca K.K., Osaka, Japan) given as continuous infusion with the rate of 160, 80, 40, 20, or 10 mg · kg^{-1} · h^{-1} (group 1, 2, 3, 4, or 5, respectively). The continuous infusions were administered by using a Graseby 3500 (Smiths Medical International, Watford, United Kingdom) infusion pump. Age (< 65 and ≥ 65 yr) and gender were stratified into all study groups.

Propofol was infused directly *via* an 18- or 20-gauge catheter in a large forearm vein without any other fluids given simultaneously. As such, the remaining dead space was limited towards the dead space of the infusion catheter (less than 0.023 ml) filled with blood before starting the propofol administration. The propofol syringe and extension line were purged and pressurized before being connected to the infusion catheter. The moment the START button was pushed was considered as time 0.

No other drugs were given during the study period. All patients received 100% oxygen *via* a facemask during the study period. When airway obstruction occurred, airway was secured gently without any stimulation.

Sample Acquisition, Handling, and Processing

A 22-gauge arterial catheter was inserted in the radial artery at the opposite site of the venous catheter for propofol infusion.

To ensure accurate blood sample quality, a continuous blood flow during the study period of around 50 ml/min was generated by using a negative pressure blood drawing device (Hemoquick®; Terumo, Tokyo, japan). Arterial blood samples (1 ml each) were drawn by using

heparine-coated 2.5-ml syringes *via* a closed-system sampling port at the arterial line (dead space 1.5 ml).

Arterial blood samples were taken at 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 s during the first 1 min in all groups. Samples were then collected every 10 s until 120, 150, or 200 s in groups 1, 2, and 3, respectively. In group 4, samples were taken at 70, 80, 90, 120, 150, 180, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, and 310 s, and in group 5 at 70, 80, 90, 120, 150, 180, 210, 240, 300, 360, 420, 430, 440, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, and 530 s. These blood samples were centrifuged within an hour of collection. The plasma was transferred to polyethylene tube and kept at −20°C until assayed.

Measuring Propofol Cerebral Drug Effect

Propofol cerebral drug effect was monitored by using the BIS, which was derived from the frontal electroencephalogram and calculated by the A-2000 BIS monitor (version 4.0; Aspect Medical Systems, Norwood, MA) by using the three BIS Sensor electrodes. The smoothening rate of the BIS monitor was set at 15 s. BIS values range from 100 to 0, with lower values denoting more drug effect.[11] The BIS values were recorded every 5 s by Bispectrum Analyzer software developed by one of the authors[12] using an RS-232C connection between the BIS monitor and a laptop computer. The end of the study period was defined as 60 s after the end of last arterial sampling time.

Drug Assay

Arterial plasma concentrations (Cp) of propofol were determined by high-performance liquid chromatography (RF-550, CTO-10AS, LC-10AD, SIL-10AD, SCL-10A, and DGU-14A; Shimadsu, Kyoto, Japan) with fluorescence detection at 310 nm after excitation at 276 nm.[13] The lower limits of detection and quantification were 1.7 and 5.6 ng/ml, respectively. Measured Cp below the lower detection limit was not applied to the model development and measured Cp between the lower limit of detection and that of quantification was considered as the half value of the lower quantification limit.

Population Pharmacokinetic Modeling

Basic Model Structure. The following structural models were evaluated; conventional 1-, 2-, and 3-compartmental models, conventional one-, two-, and three-compartmental models enlarged with LAG model, conventional one-, two-, and three-compartmental models enlarged with a TRANSIT models, and conventional one-, two-, and three-compartmental models enlarged with a LAG and TRANSIT model (fig. 1). All compartmental models had a central compartment, and one or two peripheral compartments, if necessary. The LAG time and/or the TRANSIT model describes the time required for the venously injected drug to reach the sam-
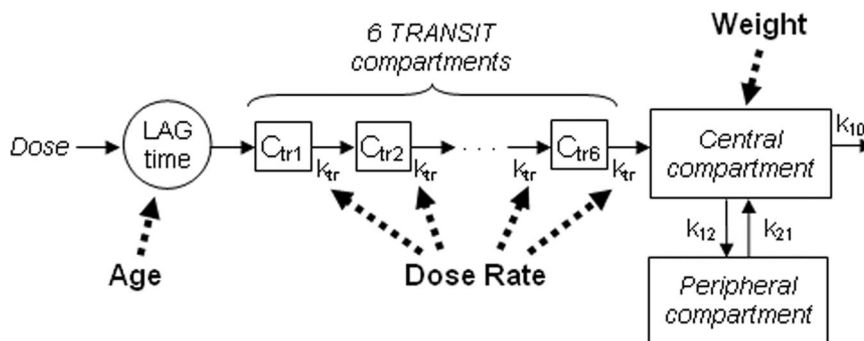
Fig. 1. Schema of the final two-compartmental pharmacokinetic model with a LAG time and six TRANSIT compartments (Ctr $_n$). The equilibration rate constants between central and peripheral compartments were calculated by using the following equations: $k_{12} = Cl_2/V_1$, $k_{21} = Cl_2/V_2$. The elimination rate constant was calculated: $k_{10} = Cl_1/V_1$. Cl_1 = clearance of central compartment; Cl_2 = clearance of peripheral compartment; LAG time = the time shift of dosing as if the drug was in fact administered to the pharmacokinetic model at a later time. TRANSIT compartments = a multiple-step process represented by a chain of presystemic compartments; V_1 = distribution volume of central compartment, V_2 = distribution volume of peripheral compartment.

pling site of arterial blood. The k_{tr} is a first-order transit rate constant describing the movement of propofol between TRANSIT compartments or TRANSIT compartment and central compartment in the TRANSIT model. The optimal number of TRANSIT compartments was assessed by stepwise addition or deletion of one TRANSIT compartment. All combinations of these models were compared.

All model parameters were estimated by using NONMEM VI (GloboMax LLC, Hanover, MD). The interindividual variability on each basic model parameter (V_1, V_2, V_3, CL_1, CL_2, CL_3, k_{tr}, and LAG time; V being the distribution volume for compartment, CL being the clearance for the compartment) was estimated by using a log-normal distribution:

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

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 $\omega.^2$ 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 was modeled by using constant coefficient of variance model and additive error model. The best model had the minimum values of Bayesian Information Criterion among the all evaluated model. These criteria were calculated by the following equations:

$$\text{Bayesian Information Criterion} = \text{OFV} + \text{K log(N)}$$

where OFV is –2 log likelihood calculated as the objective function value (OFV) by NONMEM, K is the number of parameter estimates in the model, and N is the sample size of the data set. The Bayesian Information Criterion value was used to select the best structural model because the Bayesian Information Criterion would provide a more appropriate selection than the OFV when the different structural models are compared.[14]

Covariate Assessment for Pharmacokinetic Model. The best basic structural model was implemented to assess the covariates by using a stepwise forward addition and backward elimination approach. In this process, a decrease in OFV by 7.88 ($P < 0.005$, chi-square test with 1 degree of freedom) was considered significant. When the assessed model included an additional potential covariate without an increment of the number of the parameter estimates, a decrease in OFV was considered to obtain the potential covariate into the final model. Weight, height, age, and dose rate were assessed as potential covariates when the linear regression analysis indicated significant correlation ($P < 0.05$) between a covariate and a parameter estimate. After significant regression, all potential covariates were tested on the parameters from the basic structural model (V_1, V_2, CL_1, CL_2, LAG, and k_{tr}). Correlations between mean transit time and model parameters were also calculated to assess the accuracy of the inclusion of LAG or k_{tr} into the model:

$$\text{mean transit time} = \text{LAG} + N_{tr}/k_{tr}$$

where N_{tr} is the number of transit compartments. For assessing the effects of a covariate on the model accuracy, we used not only OFV, but we also depicted the measured/predicted Cp and measured Cp *versus* time. When this figure indicated severe bias in the assessed model, we excluded the model for further consideration.

Population Pharmacodynamic Modeling
Basic Model Structure. The effect-site was assumed to be linked to the plasma by a compartment with a first-order equilibrium constant of k_{e0}. A classic sigmoidal maximum possible drug effect (E_{max}) model was used for describing the relation between propofol effect-site concentration (Ce) and the electroencephalographic measures of propofol with either measured plasma con-

centration (Cp) or predicted Cp. The time course of the predicted Cp was calculated during the pharmacodynamic modeling by using the individual patients' *post hoc* Bayesian pharmacokinetic parameters estimated in the pharmacokinetic modeling. The Ce with measured Cp was calculated by using a "connect-the-dots" approach previously used by Schnider *et al.*[15] and mathematically described previously.[6] The classic sigmoidal E_{max} model is described by the following equation:

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

where Effect is the electroencephalographic effect (*e.g.*, the measured BIS value), E_0 is the baseline measurement when no drug is present, E_{max} is the maximum possible drug effect, Ce is the calculated effect-site concentration of propofol, Ce_{50} is the Ce associated with 50% maximum drug effect, and γ is the steepness of the concentration *versus* response relation. The model parameters were estimated by using NONMEM. For Ce_{50}, k_{e0}, and γ, interindividual variability was permitted by using a log normal distribution ($\theta_i = \theta_{TV} \cdot e^{-\eta i}$, which was the same equation in the pharmacokinetic model). Interindividual variability for E_0 was expressed by using a normal distribution: $\theta_i = \theta_{TV} + \eta_i$. Interindividual variability is reported as ω, the SD of η in the standard domain for E_0. Residual intraindividual variability was modeled by using an additive error model.

In the pharmacodynamic modeling, we compared an E_{max} model with a fixed E_{max} at zero and an E_{max} model with an estimated E_{max}. Although one should be cautious with extrapolations, these two pharmacodynamic models were studied as one might criticize that the BIS might depict a maximum drug effect at a BIS value of zero. In addition, we included the BIS delay, defined as a time shift of applying the effect-site concentration to the sigmoidal E_{max} model when BIS value and the effect-site concentration were applied to the model, which reflects the time delay for the BIS measurement. This delay is the result of the combination of averaging algorithms (*i.e.*, smoothening rate), the delay caused by the BIS signal quality and the delay in adaptation of one of artifact rejection preprocessing steps.[6,16] In this study, the BIS delay was assessed as one value with no variation for all groups.

For the pharmacodynamic model approach, we assumed that the underlying sigmoidal model that describes the relation between Ce and the drug effect is not influenced by the dose rate of drug administration.

This is a fundamental assumption underlying the standard model of the effect-site. Therefore, we concurrently estimated the model parameters for all five groups, only permitting the value of k_{e0} to differ among groups.

Different K_{e0} Values for the Basic Model. We assessed the different k_{e0} for each basic structural model. When one k_{e0} was determined for two or more groups, each k_{e0} (different k_{e0}) was used for each consecutive group (*e.g.*, one k_{e0} is for groups 1 and 2, and the other k_{e0} is for groups 3, 4, and 5). The addition of k_{e0} was considered statistically significant when the NONMEM objective function value (OFV or –2 log likelihood) decreased by at least 6.63 for an additional k_{e0} ($P < 0.01$, chi-square test with one degree of freedom).

Covariate Assessment for the Pharmacodynamic Model. After the assessment of the different k_{e0}, the final pharmacodynamic model was implemented to assess for possible covariates. In this process, a significant correlation ($P < 0.05$) between a covariate and a parameter on the linear regression and a decrease in OFV by 6.63 ($P < 0.01$, chi-square test with 1 degree of freedom) was an additional criterion for a covariate. Schnider *et al.* reported that elderly patients are more sensitive to the hypnotic and electroencephalogram effects of propofol than younger persons.[15] Therefore, age was explored as a covariate for Ce_{50}.

Model Evaluation. For a basic internal evaluation of the final pharmacokinetic model, a goodness-of-fit plot was used. The plot included the correlation between individual predicted concentrations by the Bayesian estimates and measured concentrations of propofol. We also depicted measured/predicted Cp or measured/predicted BIS *versus* time that shows the bias of the prediction *versus* time.

Bootstrap analysis was used for advanced internal evaluation of both pharmacokinetic and dynamic final model. One thousand bootstrap resampling data sets for both were created by sampling data from the original data set with replacement. Sample size of resampling data sets was the same as that of original data set. The final pharmacokinetic and dynamic model, including all significant covariates, was fitted to each of the resulting data sets. Confidence intervals of 95% were obtained for each parameter estimate as the 25th and 97.5th percentiles.

Median absolute prediction error (MDAPE) and median prediction error (MDPE) were also calculated as the metrics of the accuracy by using the individual parameters (population or *post hoc* Bayesian parameters) of the

Table 1. Demographic Data, Mean ± SD (Range)

	Group 1	Group 2	Group 3	Group 4	Group 5
Age, yr	54 ± 8 (37−66)	50 ± 11 (41−72)	58 ± 7 (49−69)	60 ± 14 (36−76)	59 ± 14 (30−75)
Gender, male/female	1/9	2/8	1/9	1/9	2/8
Weight, kg	60 ± 5 (48−65)	51 ± 6 (38−57)	52 ± 7 (39−61)	52 ± 7 (45−63)	57 ± 7 (46−69)
Height, cm	155 ± 8 (138−166)	153 ± 9 (139−164)	152 ± 3 (148−158)	157 ± 5 (147−163)	155 ± 8 (146−173)

final model. For calculating these values, the following equations were used.

Percentage prediction error (PE) of the predicted CP:

$$PE = \frac{\text{measured Cp} - \text{predicted Cp}}{\text{predicted Cp}} \times 100$$

Prediction error (PE) of the predicted BIS:

$$PE = \text{measured BIS} - \text{predicted BIS}$$

PE is an indication of the bias of the achieved concentrations, and the absolute value PE ($|PE|$) is a measure of the precision (inaccuracy).
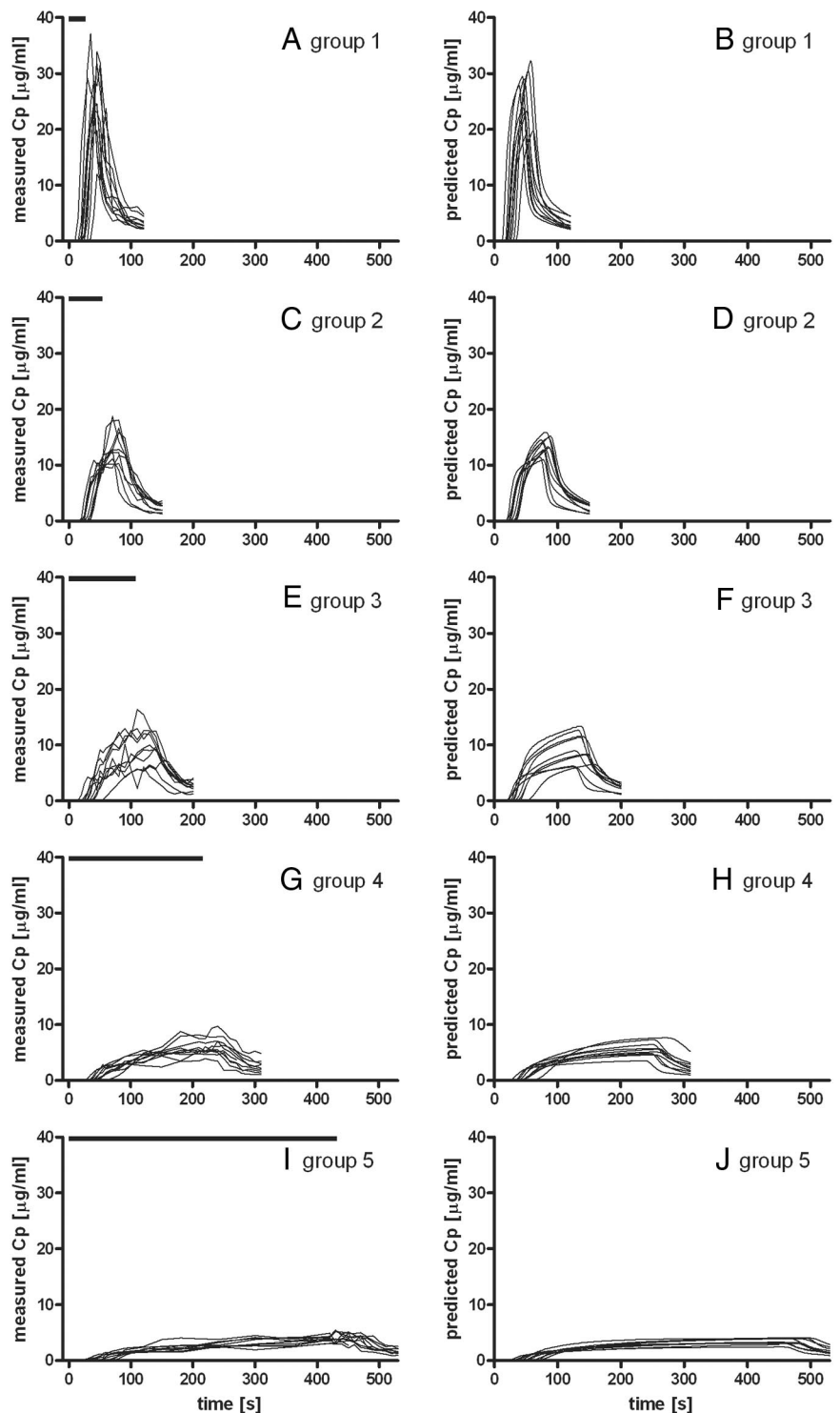
Fig. 2. Time course of measured and *post hoc* Bayesian individual predicted arterial plasma concentration (Cp) of propofol for the five groups on the *left and right panels*, respectively. Each patient received propofol of 1.2 mg/kg with the rate of 160, 80, 40, 20, or 10 mg · kg^{-1} · h^{-1} in group 1 (*A, B*), 2 (*C, D*), 3 (*E, F*), 4 (*G, H*), or 5 (*I, J*), respectively. *Bold vertical lines* on the *left panels* show the administration time of propofol.

Table 2. The Bayesian Information Criterion for the Basic Structural Pharmacokinetic Models

Number of Disposition Compartments	LAG Model	Number of Transit Compartments	Bayesian Information Criterion
1	–	0	15,755
2	–	0	–*
3	–	0	–*
1	+	0	14,744
2	+	0	14,363
3	+	0	14,369
1	–	30	14,891
2	–	30	14,344
3	–	30	14,320
1	+	6	14,723
2	+	6	14,157
3	+	6	14,159

* The measured plasma concentrations could not be fitted on the corresponding basic pharmacokinetic model because several parameters were estimated as infinitesimal or infinite. The lower value of the Bayesian Information Criterion indicates the better fit.

MDAPE indicates the inaccuracy of the Cp or BIS predictions in the i-th subject:

$$MDAPE_i = median\ \{|PE_{ij}|, j = 1, \cdots, N_i\}$$

where N_i is the number of |PE| values obtained for the i-th subject.

MDPE reflects the bias of the Cp or BIS predictions in the i-th subject:

$$MDPE_i = median\ \{PE_{ij}, j = 1, \cdots, N_i\}$$

To illustrate the final pharmacokinetic model, especially for the effect of covariates, several simulations were implemented.

Results

Pharmacokinetic Model Development

All recorded data were used. The airway was secured with gentle jaw thrust in two patients, one in the group 4 and the other in group 5, because of airway obstruction. No patient experienced hemodynamic instability during the study. The demographics for the patients in the five groups are shown in table 1.

The left column in figure 2 shows the time course of the measured Cp of propofol for the five groups, respectively. There were no samples taken after 280 s for one patient in group 4 and after 460 s for another patient in group 5 due to a protocol violation. One sample at 70 s in another patient in group 4 was not available because of a technical problem with the sample line. No samples revealed concentrations between the lower limit of detection and that of quantification.

For the basic structural model, a two-compartmental model enlarged with a LAG and TRANSIT model including six TRANSIT compartments (fig. 1) was selected as the best basic model (table 2). Linear regression analysis
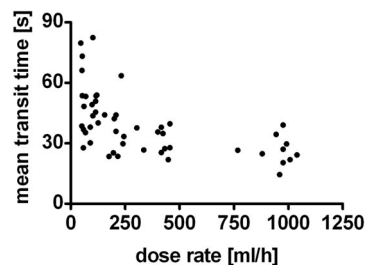

Fig. 3. Plot of the dose rate *versus* the mean transit time calculated as LAG time + $6/k_{tr}$ (k_{tr} = transit rate constant for TRANSIT compartments) by using *post hoc* Bayesian individual parameter estimates.

indicated several potential covariates, including dose rate for LAG and k_{tr}. After the visual inspection of the correlation between dose rate and mean transit time (fig. 3), we decided to test these covariates for the final model. All covariates were examined for their potential linear relationship with the structural pharmacokinetic parameters (see table, Supplemental Digital Content 1, which lists OFVs for the examined models including potential covariates, http://links.lww.com/ALN/A548). The best model includes dose rate for k_{tr}, age for LAG time, and weight for V_1 as covariates (fig. 1; see also table, Supplemental Digital Content 2, which shows the NONMEM representation of the final pharmacokinetic model, http://links.lww.com/ALN/A549). The parameter estimates in our final pharmacokinetic model are represented in table 3. Time courses of *post hoc* Bayesian predicted concentration for all patients are shown on the right column in figure 2.

Model Evaluation for the Final Pharmacokinetic Model

Figure 4 represents the goodness-of-fit plot for the measured plasma concentrations *versus* both population and *post hoc* Bayesian predicted concentrations (fig. 4A and 4B for the all groups; see also figures, Supplemental Digital Content 3, which include the goodness-of-fit plots for each group, http://links.lww.com/ALN/A550), and the time course of the measured/predicted Cp *versus* time (fig. 4C–F for all groups; see also figures, Supplemental Digital Content 3, which include the time course for each group, http://links.lww.com/ALN/A550). These figures indicate that the model provided an accurate description of the observed data. The sampling point where measured and/or predicted Cp was below quantification limit of the drug assay was excluded from figure 4C–F (see figures, Supplemental Digital Content 4, which depict the detailed information for the below limit of quantification values, http://links.lww.com/ALN/A551). On the final population model, the predicted plasma concentrations showed larger variability in the first minute than that in the later time (fig. 4E).

One thousand bootstrap runs were obtained with the same sample point at the calculating estimates of the

Table 3. Pharmacokinetic Parameters for the Final Model

Model Parameter	Value	Interindividual Variability	
		CV	95% CI
V_1, l	Weight [kg] $\cdot \theta_1$	19.3%	<1−30.4%
V_2, l	θ_2	53.2%	39.2−65.0%
Cl_1, l/min	θ_3	25.3%	20.8−28.9%
Cl_2, l/min	θ_4	48.6%	37.3−56.9%
LAG time, s	Age [yr] $\cdot \theta_5$	41.4%	32.0−48.8%
k_{tr}, /min	$\theta_6 + (DR - 345) \cdot \theta_7$	35.9%	27.2−42.8%
Parameter	Estimate	SEM	95% CI for Estimate
θ_1	0.0104	0.00180	0.00619−0.0136
θ_2	2.20	0.114	2.02−2.45
θ_3	3.20	0.0777	3.04−3.34
θ_4	4.21	0.317	3.61−4.84
θ_5	0.399	0.0153	0.370−0.431
θ_6	29.2	2.44	25.0−34.6
θ_7	0.0471	0.00789	0.0346−0.0624
Intraindividual Variability			95% CI
σ_1 [%]	15.1		14.2−15.8%
σ_2 [ng/ml]	37.9		17.9−52.8

CI = confidence interval; Cl_1 = clearance of central compartment; Cl_2 = clearance of peripheral compartment; CV = coefficient of variation calculated as $(exp(\omega^2)-1)^{0.5}$ of the variances of the corresponding η; DR = dose rate (ml/h) for 1% propofol; k_{tr} = transit rate constant; LAG time = the time shift of dosing as if the drug was in fact administered to the pharmacokinetic model at a later time; V_1 = distribution volume of central compartment; V_2 = distribution volume of peripheral compartment; σ_1 and σ_2 = the variances of interindividual variability for constant coefficient of variance model and additive error model, respectively.

final model. The number of successfully converged resamples was 798. Confidence intervals of 95% for parameter estimates are shown in table 3. The intervals for thetas exclude zero values. These results revealed that all the final estimated model parameters have acceptable typical values. MDAPE and MDPE of the final pharmacokinetic model were 23.6% and –1.4%, and 8.9% and 0.8% for population and *post hoc* prediction, respectively. These metrics indicated an acceptable bias and accuracy of the model.

Simulations with the Final Pharmacokinetic Model

We performed several simulations to show the influence of the covariates applied our final model as shown in figure 5. The influence of dose rate on the initial time course of the propofol arterial concentration as predicted by the final model is shown in figure 5B for a typical patient. Lower infusion rate results in longer time between the start of infusion and the start of increasing predicted concentration than faster infusion rate as transit rate constant (k_{tr}) also produces lag time (fig. 5B). For a typical patient, the influence of age and weight on the time course of the predicted arterial propofol concentration is plotted in figures 5D and 5F, respectively.

Pharmacodynamic Model Development

Five patients (one each in groups 1, 2, and 4 and two in group 5) were excluded because of technical problems with the BIS recordings (automatic recheck of the BIS monitor during the study period due to insufficient sensor fitting). Therefore, 45 patients were included into the pharmacodynamic analysis.

After initial attempts, we decided to use the *post hoc* Bayesian individual predicted Cp for the pharmacodynamic examinations because NONMEM failed to calculate the converged estimates with measured Cp. Applying multiple k_{e0} values into the model for different administration rates did not improve the model (see table, Supplemental Digital Content 5, which represents OFVs for the different k_{e0}, http://links.lww.com/ALN/A552). Age was not included into the pharmacodynamic model because R square values between age and the *post hoc* k_{e0} value for the models including estimated E_{max} or fixed E_{max} at zero indicated no significance ($R^2 = 0.001$ or 0.039, respectively).

Final Pharmacodynamic Model

The parameter estimates in our final pharmacodynamic model including estimated or fixed E_{max} are shown in tables 4 and 5, respectively (see table, Supplemental Digital Content 6, which is the NONMEM representation of the final pharmacodynamic model, http://links.lww.com/ALN/A553). Interindividual variability is expressed as SD for E_0 and coefficient of variation for E_{max}, Ce_{50}, and γ. The k_{e0} values were 0.414 min^{-1} or 0.404 min^{-1} for the model including estimated or fixed E_{max}, respectively. The LAG times for BIS delay corresponding to the effect-site concentration were 19.7 or 20.3 s for the models including estimated or fixed E_{max}, respectively. Figure 6 shows the measured BIS and *post hoc* individual Ce *versus* time, and the relation between the BIS values and the *post hoc* individual predicted Ce of propofol.

The sigmoid curves of the sigmoidal E_{max} model for the two final models indicates the similar relation between Ce and BIS when BIS value is more than 45 (fig. 7).
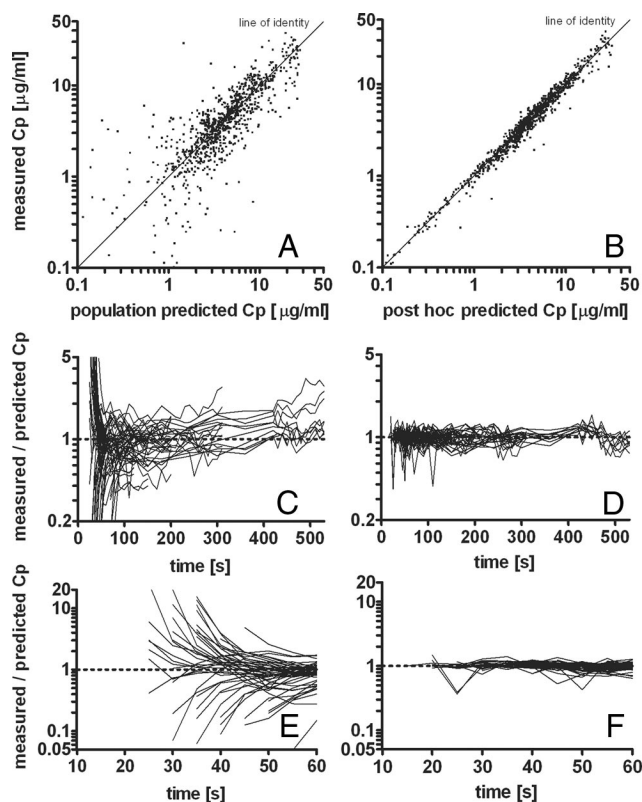
Fig. 4. Plots of the propofol predicted concentrations by population estimates (*A*) and the individual *post hoc* Bayesian estimates (*B*) of the final pharmacokinetic model *versus* measured concentrations (Cp). Measured/predicted Cp *versus* time for (*C*) population and (*D*) individual. Measured/predicted Cp *versus* time in the first 1 min using the wide scale of Y-axis compared with *C* and *D* for (*E*) population and (*F*) individual.

Pharmacodynamic Model Evaluation

For both pharmacodynamic models, figures 8A–8D show the goodness-of-fit plot for the time course of the measured/predicted BIS *versus* time. Figure 8E and 8F depict the sigmoid curve and all measured BIS value *versus post hoc* individual Ce. These figures indicate that the model provided an accurate description of the observed data.

One thousand bootstrap runs were obtained with the same sample point at the calculating estimates of the two final models. The numbers of successfully converged resamples were 891 or 904 for the models including estimated E_{max} or fixed E_{max} at zero, respectively. Confidence intervals of 95% for parameter estimates are shown in tables 4 and 5 for the two final pharmacodynamic models. These results revealed that all the final estimated model parameters have acceptable typical values. The MADPE and MDPE values of the two final pharmacodynamic models are shown in table 6 for both population and *post hoc* predictions. These metrics indicated an acceptable bias and accuracy of the model.

Correlation between Dose Rate and k_{e0}

Figure 9 shows the *post hoc* k_{e0} values *versus* the dose rate of propofol in the final pharmacodynamic model.

There were no significant differences among the groups using a Tukey multiple comparison test.

Discussion

We found that a multi-compartmental model including a LAG time and TRANSIT model described the time course of arterial propofol concentration in the first minutes after administration more accurately than a classic compartmental model. In addition, we found that the propofol administration rate influenced the early phase kinetics but not the dynamics. Age and weight were also defined as covariates in our pharmacokinetic model.

Pharmacokinetics

Conventional mammillary multi-compartment pharmacokinetic models for propofol are well accepted and form the basis for clinically applied target-controlled infusion systems. Unfortunately, these classic models insufficiently predict the time course of the arterial propofol drug concentration for the first minutes of drug administration.[6] The failure of these models is an expected consequence of a flawed assumption with conventional mammillary compartmental models of instantaneous mixing in the central compartment and immediate appearance of drug at the arterial sample side. More appropriate models are required to study the early phase kinetics, certainly in relation to possible covariates influencing these kinetics.

Before being able to analyze the influence of covariates such as the infusion rate on the dose-response of propofol, we needed the model including the delay between drug administration and appearance of the drug at the site of arterial blood sampling. Although we realized that this delay might be explained mechanistically or by physiologic phenomena such as transit delay due to passage through the forearm vein[17] and lungs,[18] it was only our intention to model the delay by using a compartmental, mathematical approach. The LAG time and TRANSIT models were previously used to describe the absorption delay in orally given drugs.[8] Upton *et al.* also used the concept of LAG time in their physiologically based model to describe the delay between the infusion site and the vascular mixing volume submodel and a TRANSIT model with three compartments in the lung submodel.[18] The recirculatory model by Avram and Krejcie also includes the chain of TRANSIT compartments for the central circulation in the model.[7] We assessed four basic structural models combining a conventional one-, two-, and three-compartmental model enlarged with the LAG time and/or TRANSIT model in an attempt to increase the accuracy of the traditional compartmental model for describing the time course of the propofol arterial concentration, especially during the first minutes of drug administration. We revealed that both LAG and TRANSIT
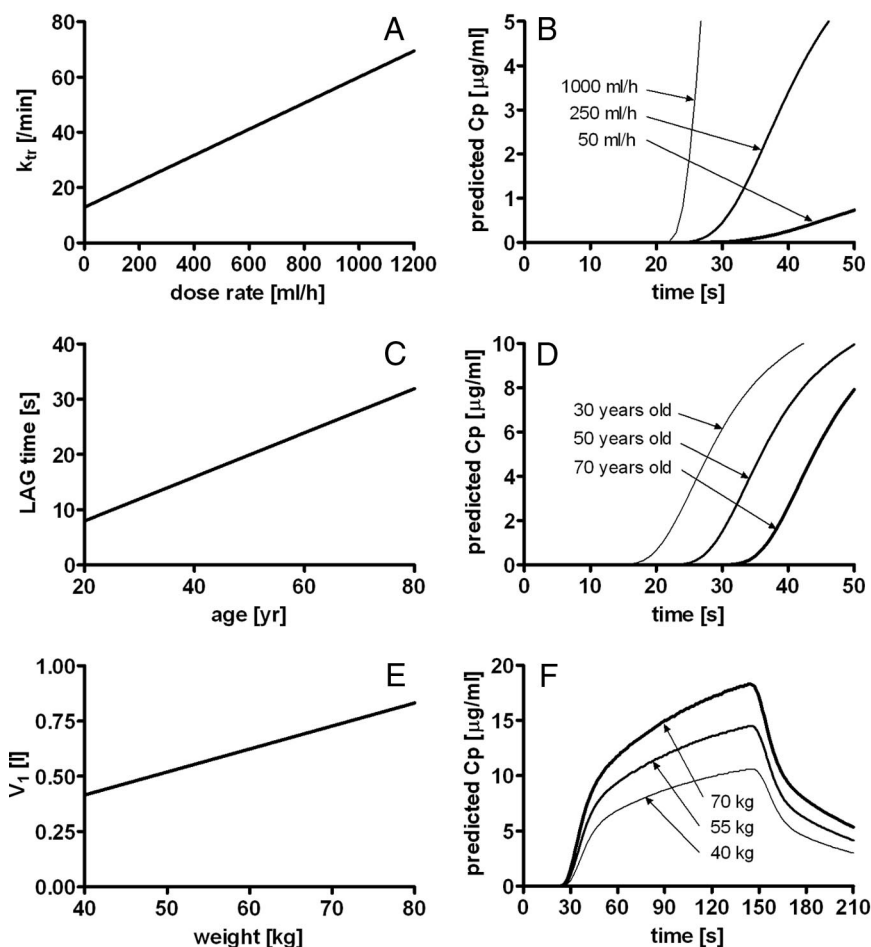
Fig. 5. Simulation with the final pharmacokinetic model and influence of covariate on model parameter: (*A*) influence of dose rate on transit rate constant (k_{tr}), (*B*) dose rate on k_{tr} for 50-yr-old, 60-kg subject with 1,000, 250, and 50 ml/h infusion of 1% propofol, (*C*) influence of age on LAG time, (*D*) age on LAG time and for 60-kg subject with 400 ml/h infusion, (*E*) influence of weight on V_1, (*F*) weight on distribution volume of central compartment (V_1) for 50-yr-old subject with 2-min 60 mg · kg^{-1} · h^{-1} infusion (dose is 2 mg/kg). Cp = plasma concentration; LAG time = the time shift of dosing as if the drug was in fact administered to the pharmacokinetic model at a later time.

compartments were required to describe our data accurately. We did not apply a physiologic model to depict the early drug disposition of propofol because this is much more complex and was not required to solve our hypothesis. However, we tried to add a recirculatory step to our compartmental model, similar to the work of Avram and Krecjie[7]; however, this did not result in a more accurate model when using our database (see figure, Supplemental Digital Content 7, which represents the examined compartmental model with recirculation-like characteristics, http://links.lww.com/ALN/A554).

The final structural model was a two-compartmental model enlarged with a LAG time and TRANSIT model. Although most previously published conventional compartmental pharmacokinetic models of propofol have three compartments,[19-21] our best basic model includes only two disposition compartments. This is because we focused on the first ten minutes to describe the early phase kinetics, especially in the first minutes. This was a study in patients, so it was considered unethical to draw more blood samples at a later time point. Thus, the time course of measured concentration of propofol excluded the information for

Table 4. Pharmacodynamic Parameters for the Final Model, When Estimating E$_{max}$

Model Parameter	Estimate (95% CI)	SEM	Interindividual Variability* SD or CV [%] (95% CI)
E_0	94.1 (93.3–94.8)	0.391	3.59 (2.77–4.17)
E_{max}	38.7 (32.5–40.5)	1.92	N/A
Ce_{50}, μg/ml	2.92 (2.61–3.28)	0.172	41.2% (27.7–52.5%)
γ	4.20 (2.98–5.65)	0.690	130% (94.5–166%)
k_{e0}, /min	0.414 (0.323–0.521)	0.0518	92.1% (67.1–133%)
Lag time for BIS delay, s	19.7 (12.7–27.6)	3.72	N/A
Intraindividual variability	3.89 (3.46–4.23)†		

BIS = bispectral index; Ce_{50} = effect-site concentration associated with 50% maximal drug effect; CI = confidence interval; CV = coefficient of variation calculated as $(exp(\sigma^2)-1)^{0.5}$ of the corresponding η; where σ is variance for the corresponding η; E_0 = baseline measurement of BIS when no drug is present; E_{max} = maximum possible drug effect; k_{e0} = equilibrium constant between plasma and effect-site; N/A = not applicable; γ = steepness of the concentration-versus-response relation.

* Interindividual variability is expressed as SD for E_0, and CV for E_{max}, Ce_{50}, and γ; † SD (95% CI).

Table 5. Pharmacodynamic Parameters for the Final Model, When Using Fixed E$_{max}$ at Zero

Model Parameter	Estimate (95% CI)	SEM	Interindividual Variability* SD or CV [%] (95% CI)
E$_0$	94.7 (94.0−95.5)	0.393	3.61 (2.61−4.22)
E$_{max}$	0	N/A	N/A
Ce$_{50}$, μg/ml	4.55 (3.46−5.43)	0.499	56.4% (37.3−73.6%)
γ	2.44 (1.90−3.54)	0.429	108% (71.9−143%)
k$_{e0}$, /min	0.404 (0.278−0.550)	0.0680	101% (63.1−167%)
Lag time for BIS delay, s	20.3 (6.99−28.3)	5.76	N/A
Intraindividual variability	4.11 (3.61−4.58)†		

BIS = bispectral index; Ce$_{50}$ = effect-site concentration associated with 50% maximal drug effect; CI = confidence interval; CV = coefficient of variation calculated as (exp(σ^2)-1)$^{0.5}$ of the corresponding η, where σ is variance for the corresponding η; E$_0$ = baseline measurement of BIS when no drug is present; E$_{max}$ = maximum possible drug effect; k$_{e0}$ = equilibrium constant between plasma and effect-site; N/A = not applicable; γ = steepness of the concentration-versus-response relation.

* Interindividual variability is expressed as SD for E$_0$, and CV for E$_{max}$, Ce$_{50}$, and γ; † SD (95% CI).

γ-phase, where half-life is over 4 h.[22] We have to accept that we only studied the early disposition of propofol; as such, our pharmacokinetic model should not be extrapolated to predict the pharmacokinetic behavior of propofol at a later stage.

Covariate analysis started by investigating the influence of dose rate on the early phase kinetics. K$_{tr}$ was influenced by dose rate as shown in table 3 and depicted in figure 5. Several other covariates were tested and
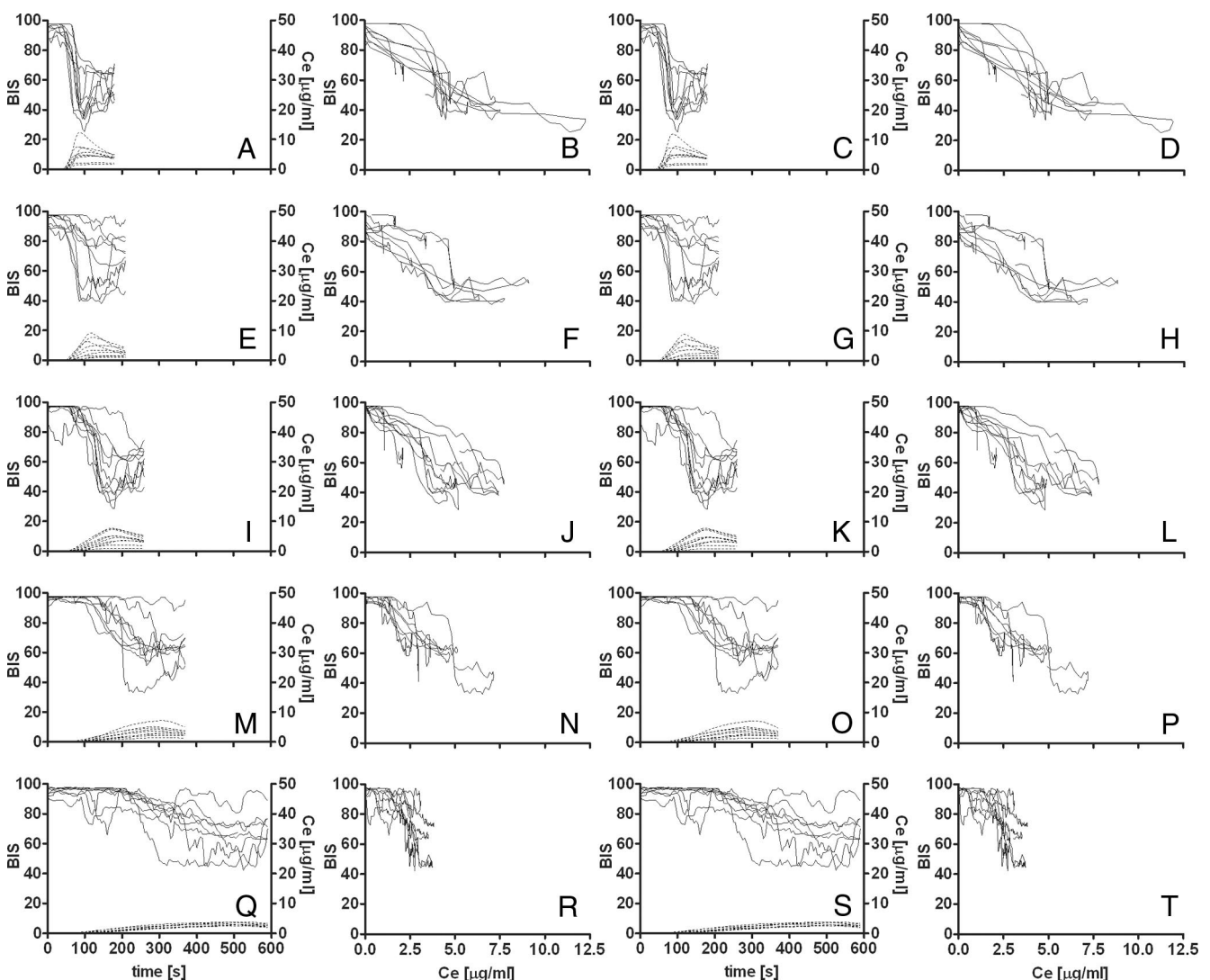

Fig. 6. Results from the final pharmacodynamic model, including estimated maximum possible drug effect (E$_{max}$) (*first column*) or fixed E$_{max}$ at zero (*third column*). Individual measured Bispectral Index (BIS) values and the *post hoc* Bayesian individual effect-site concentration (Ce) *versus* time (*first column* and the *third column*, respectively). The *second column* and *fourth column* show the BIS *versus post hoc* Ce. Each patient received propofol of 1.2 mg/kg with the rate of 160, 80, 40, 20, or 10 mg · kg^{-1} · h^{-1} in group 1 (*A–D*), 2 (*E–H*), 3 (*I–L*), 4 (*M–P*), or 5 (*Q–T*), respectively.
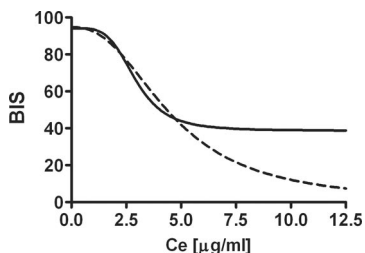
Fig. 7. Curves of the final sigmoidal maximum possible drug effect (E_{max}) models. *Bold line* and *dotted line* show the curve for estimated E_{max} and fixed E_{max} at zero, respectively. BIS = Bispectral Index; Ce = effect-site concentration.

Table 6. Prediction Error for Bispectral Index Calculated as Difference between Measured and Predicted Values of the Final Pharmacodynamic Model

	Prediction Error Estimated E_{max} = 38.7	Prediction Error Fixed E_{max} = 0
Population		
Median absolute	5.9	6.2
Median	2.2	-0.1
Post Hoc		
Median absolute	1.8	1.6
Median	0.2	0.2

E_{max} = maximum possible drug effect.

resulted in a final model, including age as a covariate for the LAG time and weight for V_1 (fig. 5). Other tested covariates didn't improve our model.

These findings are consistent with the results from He *et al.*,[23] who reported that the time before propofol or indocyanine green emerges from the central vein was approximately 13 s, despite the difference of the sampling site and when taking into account our more sensitive lower limits of detections of propofol (50 or 1.7 ng/ml, respectively). The age distribution of our study population allowed us to test the influence of age on the propofol early phase kinetics. We found that the LAG

time increased in older patients, as shown in figure 5. Although one may consider that lower cardiac output increased LAG time in older patients, there was no correlation between LAG time and cardiac output by using our data (see figures, Supplemental Digital Content 8, which show the relation between measured cardiac output and two model parameters of LAG time and transit rate constant, http://links.lww.com/ALN/A555). Others also found an influence of age on the propofol drug disposition, even when using classic multi-compartmental model without coverage of the early phase kinetics.[20]
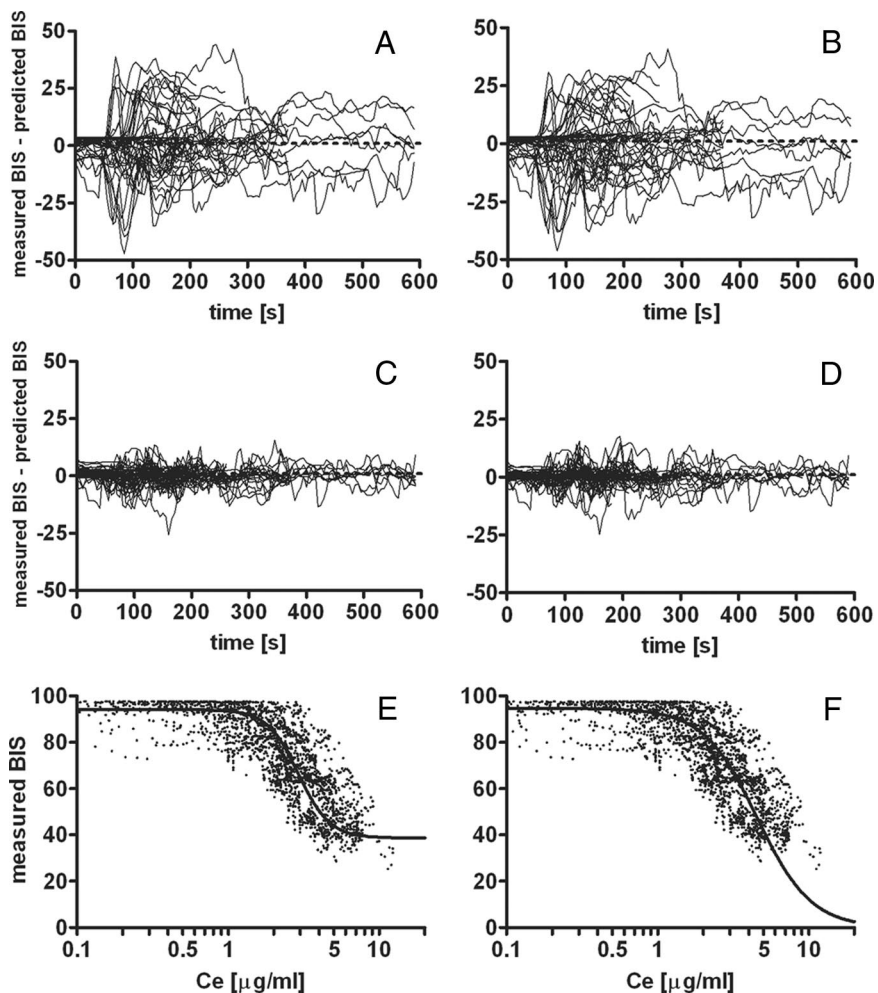

Fig. 8. Plots for the evaluation of the final pharmacodynamic model including estimated maximum possible drug effect (E_{max}) *(left panels)* or fixed E_{max} at zero *(right panels)*. Measured/predicted Bispectral Index (BIS) *versus* time is shown for population *(A, B)* and *post hoc* Bayesian individual *(C, D)* models. *(E and F)* Measured BIS *versus post hoc* effect-site concentration (Ce).
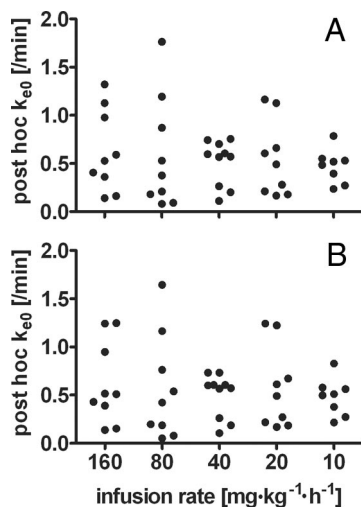
Fig. 9. *Post hoc* transit rate constant (k_{e0}) values *versus* the dose rate of propofol in the final pharmacodynamic model including estimated maximum possible drug effect (E_{max}) (*A*) or fixed E_{max} at zero (*B*).

As shown in table 3, V_1 of 0.0104 l/kg is smaller than observed by others.[19-21] When using conventional compartmental models, the central volume of distribution is dependent on the time of blood sampling and will expand with time. As such, with earlier blood sampling, one will obtain smaller central volumes. However, conventional compartmental models usually overestimate the central compartmental volume because they ignore the complexity of delay caused by intravascular mixing.[7] Weight was considered as a covariate for V_1. As the covariate analysis is fully dependent on the study population, one should be careful when comparing models from propofol because different populations might result in different model-dependent covariates.

We tested the internal validity of our model by using several analyses. As shown in figure 4, the population measured/predicted Cp *versus* time revealed the initial large variability in the population. The model bias is within acceptable limits. In addition, very large variability is observed over the first minute after the start of propofol administration, which may be partially caused by the variability of transit time from infusion site to sampling site (fig. 4C and 4E). This result indicated that our final population model was not able to address the variability in the first minute, although the high-resolution arterial samples were taken. The individual *post hoc* Bayesian propofol Cp are accurately described by the model. Figure 4 also depicts a good correlation between the individual *post hoc* Bayesian predicted arterial concentration and measured arterial concentration. As shown in table 3, the 95% confidence intervals of the parameter estimates for our model calculated by the bootstrap analysis exclude zero, revealing the accuracy of the model. In addition, all parameter estimates calculated by NONMEM are similar to the median of the estimates calculated by bootstrap analysis (data are not

shown). The MDAPE and MDPE demonstrate that the bias and the predictive inaccuracy are low for both population and individual *post hoc* Bayesian estimates. A model is expected to be accurate if the typical value of the predictive inaccuracy is less than 25%.[21] Our results indicate that our final pharmacokinetic model has an acceptable accuracy and is in the range of previous publications.[21,24,25]

Pharmacodynamics

The propofol cerebral drug effect was measured by using BIS, as applied in various previous studies.[6,26] Our pharmacodynamics could be described by using a classic sigmoid E_{max} model. As shown in figure 6, our propofol dosing strategy resulted in a significant decrease in BIS values in all groups. However, we didn't obtain BIS levels lower than 25. As such, the typical value for E_{max} in our model was 38.7. As one might criticize that we know that the BIS can go down to zero, we developed a second model fixing the E_{max} at zero. Although we accept the danger of extrapolation, figure 7 shows that both models behaved similarly above a BIS value of 45. For both pharmacodynamic models, acceptable population and *post hoc* Bayesian estimation were reached as proven by the accurate measured/predicted BIS values (fig. 8), bootstrap analysis, and MDAPE and MDPE (table 6).

When analyzing the raw data, a certain delay in the BIS behavior might be 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.[6] To take care of these delays, we included a BIS delay into our modeling work. Under accurate signal quality conditions, the average delay can in theory be estimated around 10 and 15 s. We found a typical BIS delay of 19.7 s or 20.3 s when applying the model with the estimated or the fixed E_{max}, which comes slightly longer than the theoretical delay. K_{e0} values were also similar between two pharmacodynamic models (table 4 and 5). This similarity among the models illustrated a potential of extrapolation on the model including fixed E_{max} at zero. However, one should be cautious with the possible lack of uniformity across the BIS between 100 and 0, as shown by Kreuer *et al.*[27]

To develop the pharmacodynamic model, we used the traditional two-step described by Sheiner *et al.* approach for the pharmacodynamic modeling.[9] The two-step approach is preferred in pharmacokinetics-pharmacodynamics modeling because a large number of *post hoc* parameter estimates causes the uncertainly to calculate the parameter estimates when one develops a pharmacokinetic and a pharmacodynamic model simultaneously.

Propofol transfer between the plasma and effect-site can be modeled as a first-order process characterized by k_{e0}.[9,28] The standard model of k_{e0} assumes that the rate of equilibration between the plasma and the site of drug effect is independent of the rate of drug administration; however, to the best of our knowledge, scientific valida-

tion for propofol is still incomplete. Doufas *et al.* found that induction speed is not a determinant of propofol pharmacodynamics. In their study, they applied a combined pharmacokinetic-dynamic model, whereby the pharmacokinetics were described by using a classic pharmacokinetic model. Classic pharmacokinetic models do not describe the early phase kinetics accurately; therefore, the misspecification in the pharmacokinetic model over the first few minutes might have influenced their findings.[6]

We studied whether a real influence of the propofol administration rate on k_{e0} exists. As such, we aimed at studying the influence of the administration rate on the propofol plasma-effect site equilibration using the accurate individual *post hoc* Bayesian predicted plasma concentration based on the enlarged pharmacokinetic model describing the early phase kinetics. We hereby focused on that range of infusion rates up to 1,200 ml/h available in clinically applied syringe pumps. Our final model applied one k_{e0} value for administration rates between 10 and 160 $mg \cdot kg^{-1} \cdot h^{-1}$, hereby covering the infusion rates available in commercial syringe pumps. As such, our results suggest that a model with only one k_{e0} is appropriate and can be applied during target-controlled infusion. Our conclusion that k_{e0} is independent from dose rate is also confirmed in figure 9, which depicts the relation between dose rates and the patient individual k_{e0}s. Of course, one must be careful to not extrapolate our conclusions to models including very fast bolus administration. In these manually administered bolus injections, multiple k_{e0}s might be appropriate as found previously.[6]

In conclusion, we found that a combined pharmacokinetic-dynamic model consisted of a two-compartmental model with a LAG time and TRANSIT compartments to describe the kinetics and a sigmoid E_{max} model with BIS delay to describe the dynamics is accurate and takes care of the early phase pharmacology of propofol during infusion rate between 10 and 160 $mg \cdot kg^{-1} \cdot h^{-1}$. Kinetics and dynamics could be connected with a singular k_{e0} not influenced by the propofol infusion rate. However, the early phase kinetics of propofol were influenced by the infusion rate; as such, dose rate was included as a covariate for k_{tr}. LAG time was influenced by age. In addition, although our modeling was able to handle the early phase pharmacokinetics, the large variability of population predicted plasma concentration in the first 1 min after the start of propofol infusion suggested that there may be a limit to how much pharmacokinetic models can predict the plasma concentrations against large variability of plasma concentration.

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