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Influence of Administration Rate on Propofol Plasma–Effect Site Equilibration

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Background: **The authors hypothesized a difference in plasma–effect site equilibration, depicted by a first-order constant k_{e0}, depending on the injection rate of propofol.**

Methods: **Sixty-one patients received 2.5 mg/kg propofol given as a bolus or as a 1-, 2-, or 3-min infusion. The Bispectral Index was used to monitor drug effect. Propofol predicted plasma concentration was calculated using a three-compartment model and the effect site concentration over time as the convolution between the predicted plasma concentration and the disposition function of the effect site concentration. The authors evaluated the influence of the infusion rate on the k_{e0} by comparing the model with one k_{e0} for all groups with models estimating different k_{e0} values for each group. The authors also assessed the accuracy of two pharmacokinetic models after bolus injection.**

Results: **The best model based was a fixed (Bispectral Index ≥ 90) plus sigmoidal model (Bispectral Index < 90) with two values of k_{e0}, one for the bolus ($t_{½}$ k_{e0} = 1.2 min) and one for the infusions ($t_{½}$ k_{e0} = 2.2 min). However, the tested pharmacokinetic models poorly predicted the arterial concentrations in the first minutes after bolus injection. Simulations showed the requirement for two k_{e0} values for bolus and infusion was mostly a compensation for the inaccurate prediction of arterial concentrations after a bolus.**

Conclusion: **Propofol plasma–effect site equilibration occurs more rapidly after a bolus than after rapid infusion, based on the electroencephalogram as a drug effect measure, mostly because of misspecification of the pharmacokinetic model in the first minutes after bolus.**

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PROPOFOL transfer between the plasma and effect site can be modeled as a first-order process characterized by k_{e0}.[1,2] 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, there are conflicting data on the rate of equilibration between the plasma and the site of propofol drug effect. In a study involving both bolus injections and intravenous infusions, Schnider *et al.*[3] found that the rate of equilibration was rapid, with a half-time of equilibration, $t_{½}$ k_{e0}, of 1.5 min, and a peak effect, t_{peak}, of 1.7 min. Schnider's finding of rapid equilibration was subsequently validated by Struys *et al.*[4] However, using continuous infusions of propofol, Doufas *et al.*[5] found a much slower rate of plasma–effect site equilibration, with a $t_{½}$ k_{e0} of 4.1 min, and a t_{peak} of 2.7 min. They also found that infusion rate had no influence on k_{e0}.[5]

The maximum propofol infusion rate in the study of Doufas *et al.*[5] was 60 mg/min, far lower than the maximum rate of approximately 500 mg/min required for Schnider *et al.* to give a 2.5-mg bolus over 20 s. Doufas *et al.*[5] proposed that there could be a fundamental difference in plasma–effect site equilibration depending on whether propofol was given as a bolus or continuous infusion. We investigated this hypothesis.

Materials and Methods

Clinical Protocol

After institutional ethics committee approval, written informed consent was obtained from 61 female patients with American Society of Anesthesiologists physical status I, aged 18–45 yr, scheduled to undergo ambulatory gynecologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol.

All patients were randomly assigned to one of four groups to receive 2.5 mg/kg propofol (Diprivan 1%; AstraZeneca, London, United Kingdom) given as a bolus

(within 10 s) (group 1) or given as a continuous infusion over 1, 2, or 3 min (groups 2, 3, and 4, respectively). Bolus administration was performed manually. The continuous infusions were administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France). To ensure synchronized data recording, all monitor and infusion data were continuously captured by a computer running RUGLOOP II (Demed, Temse, Belgium) *via* multiple RS 232 interfaces. By tracking the infused propofol volume continuously in groups 2, 3, and 4, RUGLOOP II calculated the corresponding plasma concentration using the three-compartment model previously published by Schnider *et al.*[6] This model was selected because of its optimal performance in previous studies.[5] For group 1, the plasma concentration was calculated *post hoc* using RUGLOOP II simulation mode and the Schnider propofol pharmacokinetic model.[6]

Propofol was infused *via* a large left forearm vein. Every patient received approximately 100 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preanesthetic medication. No other drugs were given. All patients maintained spontaneous ventilation *via* a facemask delivering 100% O_2. Before starting the drug administration, all patients were asked to close their eyes and relax for 2 min. Thereafter, baseline measures were taken. The operating room was kept silent to avoid noise-related stimulation and artifact.

Propofol drug effect was continuously monitored using the Bispectral Index (BIS; version 4.0; Aspect Medical Systems, Inc., Newton, MA). The BIS was derived from the frontal electroencephalogram and calculated by the A-2000 BIS® monitor using the four BIS®-Sensor electrodes. Electrode impedance was less than 5 kΩ. The smoothening time of the BIS® monitor was set at 15 s. The BIS data were captured in real time on a laptop computer using RUGLOOP II. Heart rate, noninvasive blood pressure, oxygen saturation measured by pulse oximetry, and capnography were recorded at 1-min time intervals using an S-5 monitor (Datex-Ohmeda, Helsinki, Finland) and were also captured electronically using RUGLOOP II. Averaging of the data was performed using 10-s intervals. All patients were monitored until return of consciousness after propofol administration, defined as spontaneous eye opening (without a stimulus).

Pharmacodynamic Modeling and Estimation of k_{e0}

In our initial approach, the effect site was assumed to be linked to the plasma by a compartment of trivial volume with a first-order equilibrium constant of k_{e0}. The relation between propofol effect site concentration (Ce) and the electroencephalographic measures of anesthetic drug effect was described using a classic sigmoid E_{max} model:

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

where Effect is the electroencephalographic effect (*e.g.*, the measured BIS), 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% maximal drug effect, and γ is the steepness of the concentration-*versus*-response relation. The model parameters were estimated using NONMEM V (GloboMax LLC, Hanover, MD). For Ce_{50} and k_{e0}, interindividual variability was permitted using a log-normal distribution:

$$P_i = P_{TV}\, e^{-\eta_i},$$

where P_i is the parameter value in the *i*th patient, P_{TV} is the typical value of the parameter in the population, and η is a random variable with a mean of 0 and a variance of ω^2. Individual variability is reported as ω, the SD of η in the log domain, which is approximately the coefficient of variation in the standard domain. Residual intraindividual variability was modeled using a standard additive error model.

After visual inspection of the BIS data above 90, and initial attempts to find a value of k_{e0} that fit all of the observations to a single pharmacodynamic model, we concluded that no model could be fit to the data. The raw BIS data showed an abrupt (< 15 s) transition from a BIS greater than 90 to a very low BIS, suggesting a nearly instantaneous state change. Therefore, we investigated the relation between propofol Ce and BIS using separate models for periods before and after the state change. The combined model described all BIS data above 90 by a single value model ("one size fits all") and all data of 90 or less using the classic sigmoid E_{max} model.

For both model approaches (classic sigmoidal model or the combined fixed plus sigmoidal model), we assumed that the underlying sigmoidal model which describes the relation between the effect site concentration and the drug effect is not influenced by the method of drug administration. Indeed, this is a fundamental assumption underlying the standard model of the effect site. Therefore, we concurrently estimated the model parameters for all four groups, only permitting the value of k_{e0} to differ between groups. We evaluated the influence of the administration rate on the k_{e0} by comparing the log likelihood between a model with one k_{e0} for all administration rates with models estimating different k_{e0} values for each group. The addition of infusion rate specific values of k_{e0} was considered statistically significant when the log likelihood decreased by at least 6.63 ($P < 0.01$, chi-square test with 1 degree of freedom).[7]

NONMEM had difficulty simultaneously estimating the

parameters of the structural model (*e.g.*, the θ parameters) and the variance model (the ω parameters). Specifically, estimating both the structural and variance models simultaneously produced highly biased estimates of the parameters, as demonstrated by the observation that the *post hoc* estimates of the η parameter were uniformly either positive or negative. Therefore, we chose the best model using the naive pooled data method as described by Kataria *et al.*[8] After identifying the best structural model, we fixed the parameters of the structural model at the naive pooled data estimates and estimated the parameters of the intersubject and intrasubject variability models. This approach comes very close to the generalized least-squares method. The generalized least-squares approach involves three steps. In the first step, the intersubject variability (*i.e.*, ω) is fixed at zero, and the typical values of the structural model (*i.e.*, θ) are estimated. In the second step, the typical values of the structural model (*i.e.*, θ) are fixed at the estimates from the first step, and the intersubject variability (*i.e.*, ω) is estimated. In the third step, the intersubject variability (*i.e.*, ω) is fixed at the value from step 2, and the typical values of the structural model (*i.e.*, θ) are estimated for the last time. Our approach was to implement the first two steps of the generalized least-squares method.

The effect site concentrations over time were calculated as the convolution of the predicted plasma concentrations over time with the disposition function of the effect site, $k_{e0}\,e^{-k_{e0}\,t}$. The convolution was based on a "connect-the-dots" approach previously used by Schnider *et al.*[3] In brief, increasing plasma concentrations were modeled using a linear interpretation between adjacent plasma concentrations. As such, when concentrations are increasing, the slope in the concentration from time t_1 to time t_2 can be modeled as

$$\text{slope} = \frac{Cp(t_2) - Cp(t_1)}{t_2 - t_1},$$

where Cp is the plasma concentration, and thus the plasma concentrations from time t_1 to time t_2 are described by the formula

$$C(t) = C(t_1) + \text{slope} \times (t - t_1).$$

The convolution of this with $k_{e0}\,e^{-k_{e0}\,t}$ calculates the effect site concentration at time t_2 as a function of the effect site concentration at time t_1 and the plasma concentrations over the interval

$$Ce(t_2) = Ce(t_1)e^{-k_{e0}(t_2 - t_1)} + (t_2 - t_1)\,\text{slope} + \frac{(k_{e0}C(t_1) - \text{slope})\,(1 - e^{-k_{e0}(t_2 - t_1)})}{k_{e0}}.$$

Similarly, when concentrations are decreasing, the slope of the log of the concentrations from time t_1 to time t_2 can be modeled as

$$\text{slope} = \frac{\text{Log}\,(Cp(t_2)) - \text{Log}\,(Cp(t_1))}{t_2 - t_1},$$

and thus the plasma concentrations from time t_1 to time t_2 are described by the formula

$$C(t) = C(t_1)e^{\text{slope} \times (t - t_1)}.$$

The convolution of this with $k_{e0}\,e^{-k_{e0}\,t}$ calculates the effect site concentration at time t_2 as a function of the effect site concentration at time t_1 and the plasma concentrations over the interval

$$Ce(t_2) = Ce(t_1)e^{-k_{e0}(t_2 - t_1)} + \frac{C(t_1)k_{e0}\,(e^{\text{slope} \times (t_2 - t_1)} - e^{-k_{e0}(t_2 - t_1)})}{k_{e0} + \text{slope}}.$$

The observed BIS value has a time delay for the measurement, which we fixed at 10 s and defined as lag time. This lag time is approximately the sum of half of the smoothing interval within the BIS® monitor and the time for the automated data collection.

We assessed the model performance by calculating the prediction error (PE) between measured (BIS_{meas}) and *post hoc* Bayesian predicted BIS (BIS_{pred}) values, as

$$PE = (BIS_{meas} - BIS_{pred})/BIS_{pred}.$$

We also calculated median prediction error (MDPE) and absolute median prediction error, (MDAPE), for each patient.[9] Differences among groups for MDPE and MDAPE were tested using a Student *t* test with Bonferroni correction for multiple testing.

To observe whether the model reflects reality, we compared the observed time of maximum BIS response ($t_{max,BIS}$) with the time to reach maximum Ce ($t_{max,Ce}$) after the specific administration of propofol in each group.

Bolus Validation Study

The three-compartment pharmacokinetic model published by Schnider *et al.*[6] was used to predict the time course of the propofol plasma concentration in our study. For slowly administered continuous infusion of propofol, Doufas *et al.*[5] found that the pharmacokinetic model published by Schnider *et al.*[6] accurately predicted the propofol plasma concentrations in arterial blood. However, the accuracy of this model in the first 3 min after bolus injection is not described in the literature.

We therefore performed a study to validate the pharmacokinetics after bolus injection. In this study, we collected propofol arterial blood samples from 10 additional patients to evaluate the accuracy of the pharmacokinetic models published by Schnider *et al.*[6] and by Marsh *et al.*[10] in the first 5 min after intravenous propofol bolus. After additional ethics committee approval and

Table 1. Demographic Data (Mean ± SD)

	Group 1 (n = 14)	Group 2 (n = 16)	Group 3 (n = 16)	Group 4 (n = 15)
Age, yr	34 ± 5	34 ± 4	33 ± 6	34 ± 6
Weight, kg	65 ± 11	65 ± 10	62 ± 8	66 ± 11
Height, cm	169 ± 7	169 ± 7	169 ± 4	167 ± 11

written informed consent, 10 patients received a bolus dose of propofol (2.5 mg/kg) within 10 s in a large forearm vein. Propofol arterial blood samples were collected (contralateral from the injection of propofol) at 0, 30, 60, 120, 180, 240, and 300 s after injection. Propofol (bound and free) plasma concentrations were analyzed using a validated gas chromatographic–mass spectrometric method with solid-phase micro extraction. The time course of the propofol plasma concentration as predicted by both pharmacokinetic models (Schnider and Marsh) was simulated using RUGLOOP II. We calculated the PE of the predicted concentration and the MDAPE for both models for the first 5 min after injection.

The arterial concentrations in the first 5 min after bolus injection were compared with the predictions based on the pharmacokinetics reported by Schnider *et al.*[6] and by Marsh *et al.*[10] As described in the Results, neither pharmacokinetic parameter set accurately predicted the concentrations in the first 5 min after bolus injection. To see whether this misspecification might affect the estimation of k_{e0}, we calculated the effect site concentrations over time after bolus injection as a convolution of the median concentrations in these 10 individuals with $k_{e0}\, e^{-k_{e0}\, t}$, the disposition function of the effect site. We then calculated the value of k_{e0} that predicted the observed time of peak BIS response.

Validation of the Applied Lag Time in the BIS Measurement

We fixed the lag time of the BIS at 10 s. Based on literature reports,[11] a longer lag time might be more appropriate. Therefore, we applied a *post hoc* analysis on our final selected model in an attempt to explore whether longer lag times would result in a better model for both the sigmoidal model and the fixed BIS plus sigmoidal model. Lag times between 10 and 25 s were evaluated, and the NONMEM objective functions were compared.

Validation of the Modeling Methods Using Another Data Set

We validated our final model results against the data previously published by Doufas *et al.*[5] In brief, Doufas *et al.* analyzed the pharmacokinetics and pharmacodynamics of propofol in 18 healthy volunteers receiving five consecutive target-controlled propofol infusions. During each infusion, predicted Ce increased linearly at a rate of 0.1, 0.3, 0.5, 0.7, or 0.9 $\mu g \cdot ml^{-1} \cdot min^{-1}$ based on the Schnider pharmacokinetic–pharmacodynamic model. BIS was collected continuously during the infusions. Doufas *et al.*[5] fit a combined pharmacokinetic–dynamic model to their data. To describe the pharmacodynamics of propofol, a classic sigmoid E_{max} model was used. No lag time in the BIS was included in the model. The study results can be seen in the original publication.[5]

We validated four models: (1) a sigmoid E_{max} model without a lag time (same as the model used in the Doufas article; (2) a sigmoidal E_{max} model with a 10-s lag time (equivalent to our sigmoidal E_{max} model); (3) a model consisting of a fixed estimate of BIS values of 90 or greater and a sigmoidal E_{max} model for BIS values less than 90, with no lag time; and (4) a model consisting of a fixed estimate of BIS values of 90 or greater and a sigmoidal E_{max} model for BIS values less than 90, with a 10-s lag time (equivalent to our best model). We encountered identical problems with concurrent identification of the structural and variance models that we described when fitting our own data, and so we used the naive pooled data approach to identify the best model among the four structural models considered. After identification of the best structural model, we fixed the structural parameters and estimated the interindividual variability.

We assessed the performance of the optimal model by calculating the PE between BIS_{meas} and BIS_{pred} values, as well as the MDPE and MDAPE for each patient.[9]

Results

Model Estimation and Validation

All recorded data were used. No patients experienced hemodynamic or respiratory instability during the study. The demographics for patient in the four groups are shown in table 1. The amount of propofol given and the infusion rates are shown in table 2.

Figures 1A–D show the relation between the measured BIS and calculated plasma concentrations, Cp, *versus* time for the four groups, respectively. The dashed line

Table 2. Administration Characteristics for Propofol (Mean ± SD)

	Group 1 (n = 14)	Group 2 (n = 16)	Group 3 (n = 16)	Group 4 (n = 15)
Propofol dose, mg	162 ± 29	162 ± 24	154 ± 19	163 ± 28
Administration time, s	6.3 ± 3.3	60 ± 0	120 ± 0	180 ± 0
Administration rate, ml/h	10,979 ± 4,310	976 ± 147	462 ± 58	327 ± 57

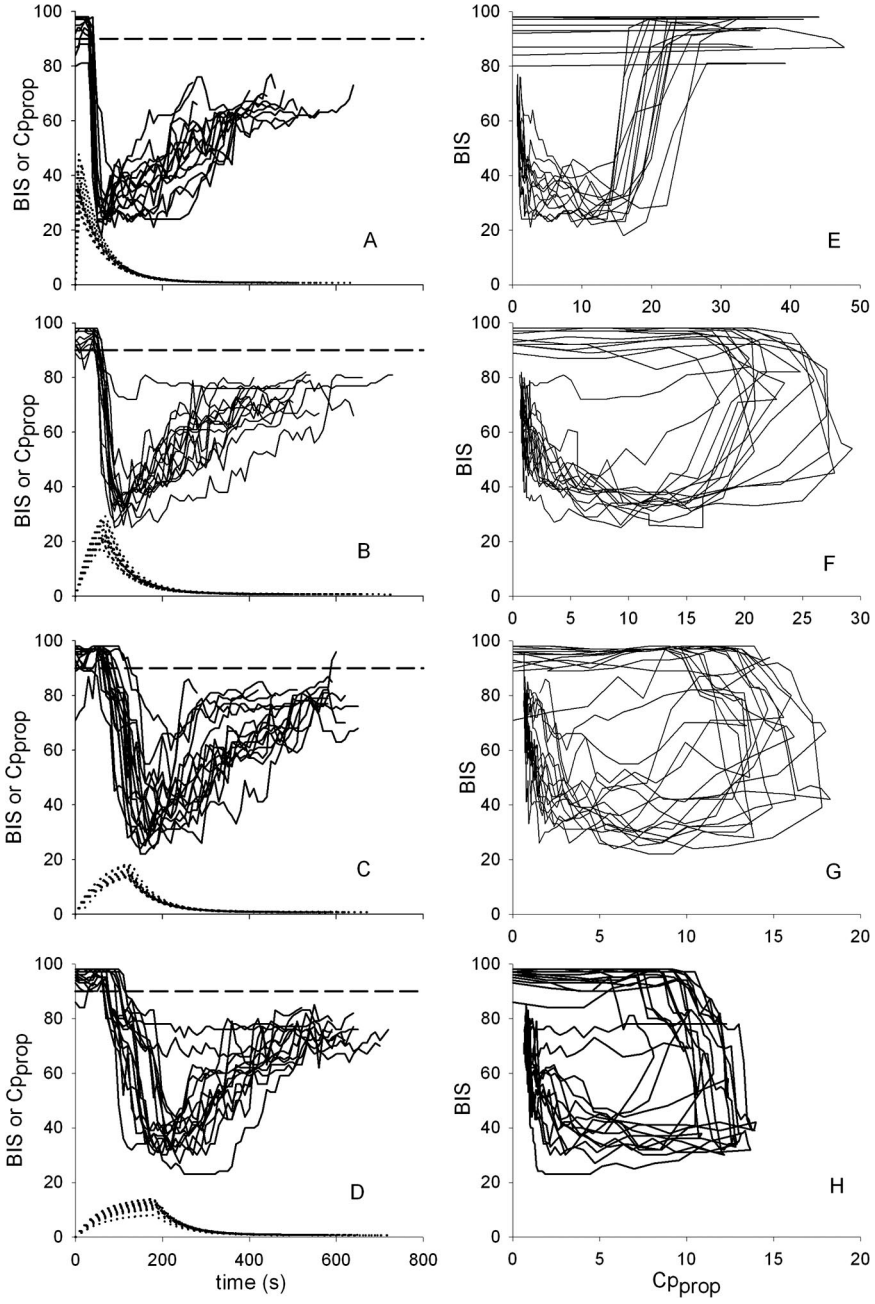

Fig. 1. Relation between the measured Bispectral Index (BIS) and propofol plasma concentration (Cp_{prop}) *versus* time (s) for the four groups, in *A–D*. The *dashed line* shows the cutoff value for modeling when the two consecutive model approach was used (fixed ≥ 90, sigmoidal < 90), fixed at a BIS of 90. *E–H* show the relation between BIS and Cp, thereby revealing the hysteresis in the relation.

shows the cutoff value of 90 used in the combined fixed plus sigmoidal model approach. Figures 1E–H show the relation between BIS and plasma concentration, revealing the hysteresis in the plasma concentration–*versus*–response relation.

Table 3 shows the NONMEM objective function (−2 log likelihood) for all investigated models. The NONMEM objective function improved by 46 points ($P << 0.001$) when the bolus group (group 1) was given a k_{e0} distinct from the k_{e0} used for the three infusion groups (groups 2, 3, and 4). There was no significant benefit to adding distinct values of k_{e0} for the three infusion

Table 3. The NONMEM Objective Function (−2 Log Likelihood) for the Different Pharmacodynamic Models Investigated

Structural Model	Sigmoidal	Fixed ≥ 90, Sigmoidal < 90
One k_{e0} estimation for all groups	18,990	19,013
Separate k_{e0} estimations for bolus injection and the three infusion groups	18,944	18,773
Separate k_{e0} estimations for bolus, 1 min infusion, and 2 + 3 min infusion	18,942	18,768
Separate k_{e0} estimations for all four groups	18,942	18,767

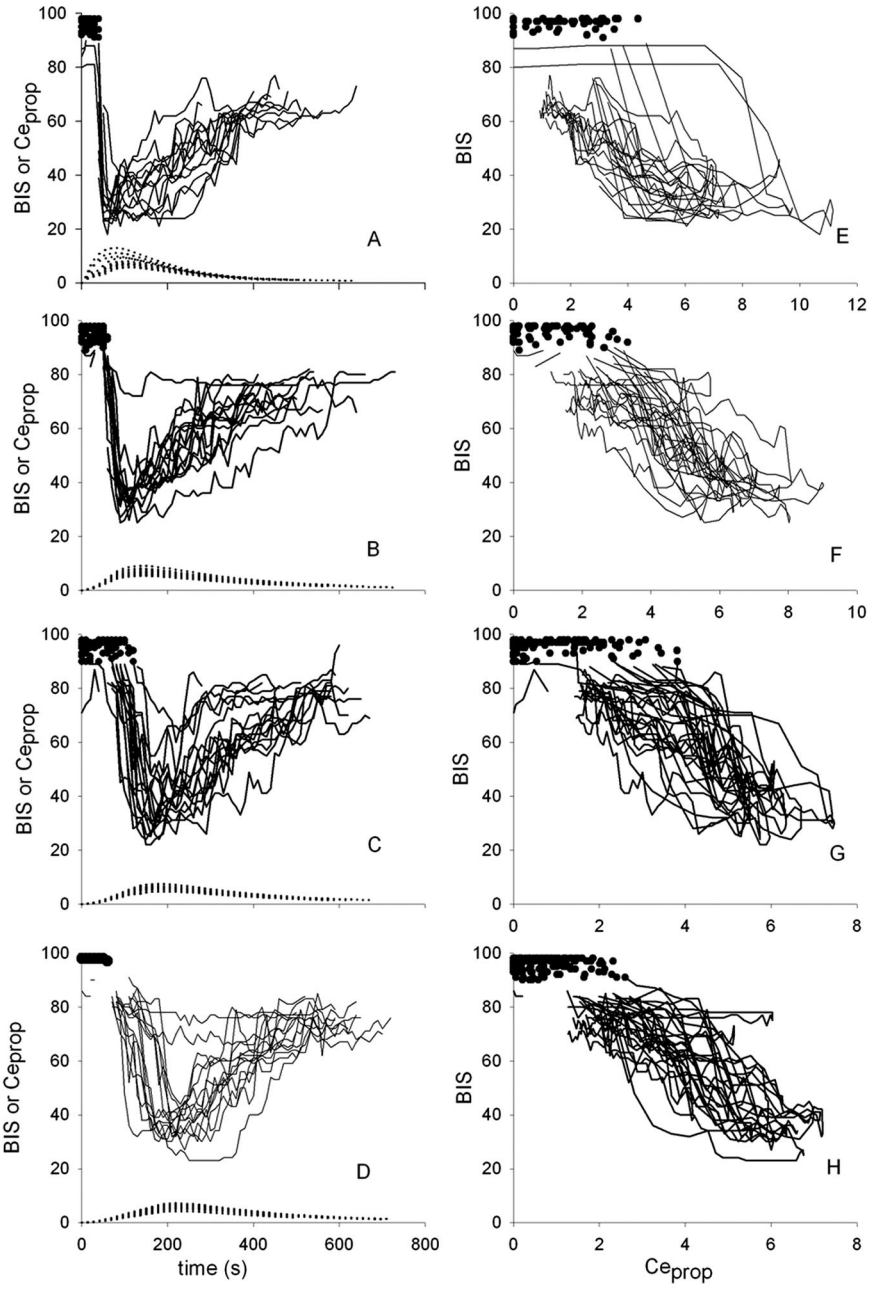

Fig. 2. Results from the best-fitting model (including estimates of interindividual variability on k_{e0} and effect site concentration associated with 50% maximal drug effect [Ce_{50}]). Individual measured Bispectral Index (BIS) values and the calculated Ce *versus* time for the four groups, in *A–D*. *E–H* show the BIS *versus* Ce, based on the k_{e0} estimate by NONMEM. To visualize the source data and results for the fixed number model, we showed the measured BIS data ≥ 90 as *black circles*. The second part (the sigmoid E_{max} model using BIS < 90) data are shown as *straight lines*.

groups. Therefore, we selected the model with two values of k_{e0}, one for the bolus ($t_{½}$ k_{e0} = 1.2 min) and one for the infusions ($t_{½}$ k_{e0} = 2.2 min).

Our final model included estimates of interindividual variability on k_{e0} and Ce_{50}. In our final model, BIS values of 90 or greater were typically 95.6. BIS values less than 90 were described by a sigmoidal curve with ranging from a maximum value of 74 to a minimum of 25. The Ce_{50} for the sigmoidal portion was 5.1 μg/ml, with a γ of 3.4. The SDs in the log domain of Ce_{50} and k_{e0} were 0.27 and 0.83, respectively, which approximately correspond to the coefficient of variation in the standard domain. Additive residual intraindividual error was 7.2.

Figures 2A–D show the raw BIS values and the calculated effect site concentration, Ce, *versus* time, showing the parallel between the time course of BIS and Ce. Figures 2E–H show the BIS *versus* Ce. BIS values of 90 or greater are depicted as black circles. BIS values less than 90 are shown as connected lines. Two individuals receiving the bolus injection had baseline BIS values below 90 (fig. 2E), which escaped our efforts to censor the initial unresponsive portion of the BIS response. We did not decrease our censoring value (90) to censor these data because we did not wish to lose informative BIS values in other subjects.

Table 4 shows the median (range) results for the *post hoc* Bayesian estimates of Ce_{50} and $t_{½}$ k_{e0} for each individual in the four groups. Table 4 also shows the time of maximum BIS change ($t_{max,BIS}$), the time of maximum Ce ($t_{max,Ce}$) after the specific propofol infusion, and the

Table 4. Median (Range) for the Individual Ce_{50}, $t_{½}$ k_{e0}, $t_{max,BIS}$, and $t_{max,Ce}$ in Each Group

	Ce_{50}	$t_{½}$ k_{e0}	$t_{max,BIS}$	$t_{max,Ce}$	$t_{abs,error}$	MDPE	MDAPE
Group 1	3.7 (5.1)	1.6 (3)	1.9 (1.2)	1.7 (0.5)	0.2 (0.9)	−0.15 (0.31)	0.18 (21)
Group 2	5.7 (9.1)	2.9 (4.5)	1.7 (0.9)	2.3 (0.3)	0.6 (1)	0.08 (0.36)	0.11 (0.18)
Group 3	5.1 (6.3)	2.2 (2.3)	2.7 (1.6)	3 (0.2)	0.4 (0.9)	0.02 (0.49)	0.1 (0.25)
Group 4	5.4 (10)	2.5 (1.9)	3.7 (1.4)	3.7 (0.1)	02 (0.7)	0.05 (0.36)	0.09 (0.17)

BIS = Bispectral Index; Ce = effect site concentration; Ce_{50} = effect site concentration associated with 50% maximal drug effect; MDAPE = median absolute prediction error; MDPE = median prediction error.

absolute value of the difference between these times (t_{error}). The difference in the time of maximum BIS change and the time of the highest Ce can be used to assess the performance of the model. The median t_{error} was 0.6 min or less for all groups. For all patients, the individual results for the *post hoc* Bayesian estimates of Ce_{50} and $t_{½}$ k_{e0} in the four groups, $t_{max,BIS}$ and $t_{max,Ce}$ after the specific propofol infusion, and the absolute value of the difference between these times ($t_{abs,error}$) can be found in a supplement on the ANESTHESIOLOGY Web site (http://www.anesthesiology.org).

The performance accuracy for the final model was assessed by calculating the PE. Figures 3A–D show the individual PE *versus* time for the four groups, respectively. Median (range) MDPE and MDAPE for each group was calculated as shown in table 4. The MDAPE was 18% or less for all groups. No group showed significant bias (MDPE). All individual MDPE and MDAPE calculations can be found on the ANESTHESIOLOGY Web site (http://www.anesthesiology.org).

Bolus Validation Study

Ten female patients were included, and all blood samples were analyzed. Demographics were similar in study groups 1 through 4 (age, 34 ± 8 yr; weight, 63 ± 10 kg; height, 163 ± 7 cm). For both models, measured *versus* predicted propofol plasma concentrations and individual PE% *versus* time are plotted in figure 4. The mean (SD) PEs were −40.50 (53.08) and −25.90 (36.80)% for the Marsh and Schnider models, respectively. The mean MDAPEs were 60.22 (28.24) and 39.45 (21.38)% for the Marsh and Schnider models, respectively.

Figure 5 shows the median arterial concentrations from the bolus. The effect site concentrations were computed based on a $t_{½}$ k_{e0} of 2.0 min and predict a peak effect site concentration of 1.9 min, consistent with the time of peak BIS effect in our bolus study (table 4, group 1). All data can be found on the ANESTHESIOLOGY Web site (http://www.anesthesiology.org).

Validation of the Applied Lag Time in the BIS Measurement

Table 5 shows the −2 log likelihood values (the NONMEM objective function) when applying different lag times. The best result is obtained when implementing a 10-s lag time in the combined fixed plus sigmoidal model approach.

Method Validation

All data from the 18 volunteers in the original publication by Doufas *et al.* were included in the model validation. Figure 6A shows the relation between BIS and Cp for the Doufas validation data set. Table 6 shows the −2 log likelihood values (the NONMEM objective function) and the typical values for all investigated models. Doufas' data were best described by a single estimate for those BIS observations of 90 or greater, and a sigmoidal E_{max} model for BIS values less than 90, with a 10-s delay, exactly as was the case for our data. Most critically, this model estimated a $t_{½}$ k_{e0} of 2.1 min, very close to our

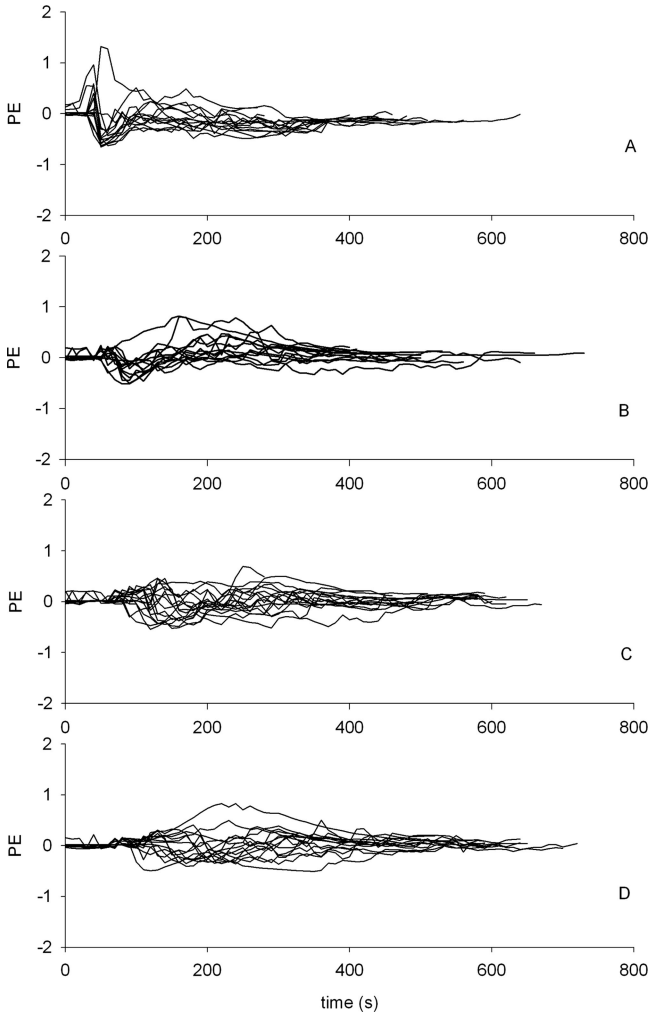

Fig. 3. Individual prediction errors (PEs) *versus* time for the four groups, in *A–D*.

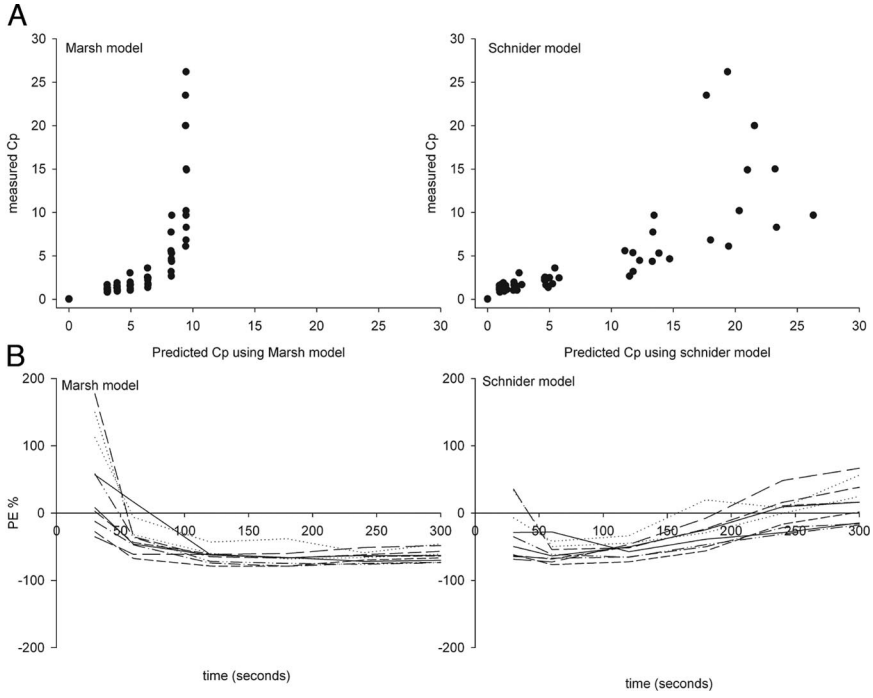

Fig. 4. The bolus injection validation set. The relation between the individual measured propofol plasma concentration (Cp) and the plasma concentration predicted by the Marsh and Schnider pharmacokinetic models (*A*). The time course of the prediction error (PE%) for both applied models (*B*).

estimate of 2.2 min for infusions. The SDs in the log domain of Ce_{50} and k_{e0} were 0.31 and 1.29, respectively. Additive residual intraindividual error was 9 (*i.e.*, residual variance = 81).

Figure 6B shows the relation between BIS and Ce for each individual, based on the best model and the *post hoc* Bayesian estimates of Ce_{50} and k_{e0}. The individual PEs are shown in figure 6C.

The median (range) *post hoc* Bayesian parameter estimates for all subjects in the validation data set are shown in table 7, as well as the individual MDPE and MDAPE. The model performed well, with an MDAPE less than 9% and minimal bias (5%). The Ce_{50} in the validation set is less than in our data set (3.6 *vs.* 5.1 μg/ml) but is similar to that seen in our bolus group (3.7 μg/ml; table 4). The estimate of γ in the validation set is less than in our data set (1.3 *vs.* 3.4). For all patients, individual data can be found on the ANESTHESIOLOGY Web site (http://www.anesthesiology.org).

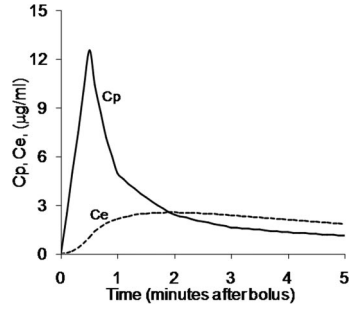

Fig. 5. The median plasma concentrations (Cp) from the 10 patients in the bolus validation study, and the effect site concentrations (Ce) predicted by a $t_{½}$ k_{e0} of 2.0. The time of peak effect, 1.9 min, matches the median time of peak Bispectral Index in the bolus study (table 4).

Discussion

Our goal was to determine whether the equilibration rate between plasma and effect site was influenced by rate of propofol administration. If so, this must be considered when designing drug infusions, and is particularly relevant for target-controlled infusion systems. We tested this by examining the time course of electroencephalographic (BIS) response to a bolus and three infusion rates. The apparent plasma–effect site equilibration for bolus injections is faster than for infusions. This is consistent with the hypothesis of Doufas *et al.*,[5] who speculated that this might be the explanation for the difference between plasma–effect site equilibration in their study *versus* the study by Schnider *et al.*[3] The accuracy of the pharmacodynamic models is demonstrated by the reasonable values of MDAPE and the agreement between the observed time to maximum BIS changes and the calculated time to the highest effect site concentration after a specific propofol administration (depending on the group).

Because this study aimed at answering the question of why different k_{e0}s are found in the literature, even when using the same pharmacokinetic model, we wanted to

Table 5. The NONMEM Objective Function (−2 Log Likelihood) When Implementing Different Lag Times in the Final Sigmoidal and Fixed plus Sigmoidal Model

Lag Time, s	Sigmoidal Model	Fixed + Sigmoidal Model
10	18,994	18,774
15	18,947	18,824
20	18,963	18,876
25	19,006	18,920

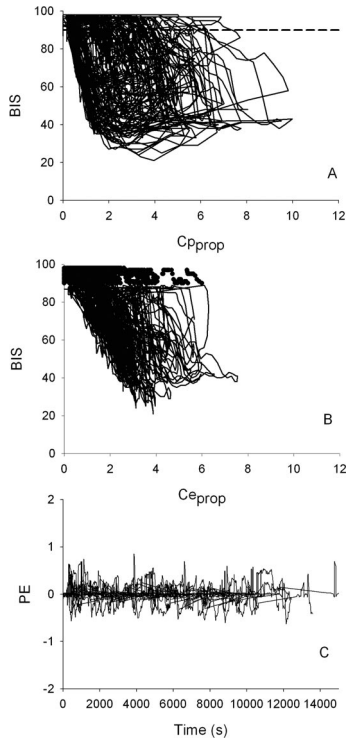

Fig. 6. The validation data set. *A* shows the relation between the measured Bispectral Index (BIS) and propofol plasma concentration (Cp_{prop}). *B* shows BIS *versus* effect site concentration (Ce_{prop}), based on k_{e0} estimate by NONMEM. To visualize the source data and results for the fixed number model, we showed the measured BIS data ≥ 90 as *black circles*. The second part (the sigmoid E_{max} model using BIS < 90) data are shown as *straight lines*. *C* shows the individual prediction error (PE) from the best fitting model (fixed ≥ 90, sigmoidal < 90, 10-s delay; including estimates of interindividual variability on k_{e0} and Ce_{50}).

explore bolus injections (as used by Schnider *et al.*[3]) and various infusion rates covering published work and clinical practice. Our bolus was 2.5 mg/kg given over 10 s. Our slowest administration was an infusion of 2.5 mg/kg given over 3 min, which is 50 $mg \cdot kg^{-1} \cdot h^{-1}$. This is lower than the critical infusion rate of 80 $mg \cdot kg^{-1} \cdot h^{-1}$ that Kazama *et al.*[12] postulate causes incomplete mixing in the central compartment.

Classically, the sigmoid E_{max} model has been applied successfully for pharmacodynamic modeling of propofol. However, when observing our raw BIS data, we found that the BIS values showed no change during the initial increase in effect site propofol concentration, until there was an abrupt decrease. This may reflect an acute change in BIS with loss of consciousness, although the article by Doufas *et al.* examined BIS at loss of consciousness and did not detect any abrupt state change. This might be due to the fact that they used an Observers' Assessment of Anesthesia/Sedation score of less than 2 (= loss of responsiveness to shaking and shouting) as their endpoint.[5] Alternatively, this delay may reflect the combination of the averaging algorithm to calculate BIS (*i.e.*, smoothing rate) and the delay in adaptation of one of the artifact rejection preprocessing steps, that rejects large changes in the electroencephalogram as artifact until those changes persist for approximately 5 s (Scott Greenwald, Ph.D., Vice President of Research, Aspect Medical Systems, Newton, MA, verbal personal communication, April 2005). We found that the inclusion of a lag time of 10 s into our model resulted in the best fit. Longer lag times resulted in worse fits of the model to the data. Regardless, the initial observations when the BIS was unambiguously unresponsive to changing propofol concentrations (figs. 1E–H) were censored from the sigmoidal model by introducing a separate model for BIS values of 90 or greater and BIS values less than 90. This model significantly improved the quality of the fit with our data ($P << 0.001$ for the 2 k_{e0} model; table 3) and with the validation data set from Doufas *et al.*[5] ($P << 0.001$ for the models with 10-s delays; table 6).

If propofol administration rate is influencing the time course of drug effect, a model incorporating different estimates of k_{e0} for different infusion rates would yield a better model fit than a model whereby one k_{e0} was used to describe the time course of effect site concentration independent of drug administration rate. We found that the model discriminating the bolus injection group from the three continuous infusion groups yielded a significantly better fit than a model with a single k_{e0} for all four groups. In our bolus group, the value of $t_{½}$ k_{e0} was 1.2 min, very close to the value of 1.5 min reported by

Table 6. Validation Modeling Using the Data Set Previously Published by Doufas *et al.*[5]

	Sigmoid Model, No Delay	Sigmoid Model, 10-s Delay	Fixed ≥ 90, Sigmoidal < 90, No Delay	Fixed ≥ 90, Sigmoidal < 90, 10-s Delay
−2 Log likelihood	37,498	37,379	35,087	34,952
Average BIS for values ≥ 90	NR	NR	95.5	95.5
Ce_{50}	2.8	2.8	3.6	3.6
γ	1.4	1.4	1.2	1.3
E_0	100	100	90	90
E_{max}	25	25	25	25
$t_{½}$ k_{e0}, min	3.4	3.1	2.2	2.1
k_{e0}, min^{-1}	0.20	0.22	0.32	0.34

BIS = Bispectral Index; Ce_{50} = effect site concentration associated with 50% maximal drug effect; E_0 = baseline measurement when no drug is present; E_{max} = maximum possible drug effect; γ = steepness of the concentration-*versus*-response relation; NR = not relevant.

Table 7. Median (Range) Individual Ce_{50}, $t_{½}$ k_{e0}, MDPE, and MDAPE for Each Individual Subject, TV with CV in the Doufas Validation Data Set, Using the *Post Hoc* Bayesian Estimates of the Best Model*

	Ce_{50}	$t_{½}$ k_{e0}	MDPE	MDAPE
Median (range)	3.68 (8.28)	1.51 (1.5)	0.007 (0.171)	0.060 (0.129)
TV	3.63	2.06	NA	NA
CV, %	31	129	NA	NA

* Fixed ≥ 90, sigmoidal < 90, 10-s delay.

Ce_{50} = effect site concentration associated with 50% maximal drug effect; CV = coefficient of variation; MDAPE = median absolute prediction error; MDPE = median prediction error; NA = not applicable; TV = typical population value.

Schnider *et al.*,[3] whose value of k_{e0} was primarily based on bolus propofol administration. In the Schnider study, the bolus was administered in a mean time of 18 s (range, 13–24 s), which is somewhat slower than in our study (table 2). In addition, our calculated time of maximum BIS effect in the bolus group was 1.7 min (table 4), exactly the same as reported by Schnider *et al.*[3] Our $t_{½}$ k_{e0} of 2.2 min for propofol administration by infusion is in agreement with the value computed from the validation data set of Doufas *et al.*[5] of 2.1 min, both of which reflect fast infusions, but obviously less rapid than bolus injections.

Our findings are consistent with propofol modeling studies using a conventional continuous infusion, which have reported propofol $t_{½}$ k_{e0}s between 2.3 and 3.5 min. In the first commercial target-controlled infusion device (Diprifusor; AstraZeneca), the kinetic model described by Marsh *et al.*[10] was linked to a $t_{½}$ k_{e0} of 2.65 min as described by Schwilden *et al.*[13] and based on slow continuous infusion data. Billard *et al.*[14] administered propofol (continuous infusion of 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ until burst suppression) and measured the electroencephalographic effect using three different electroencephalographic measures. The estimates of $t_{½}$ k_{e0} were significantly higher (mean, 2.6 min) for delta power than those for spectral edge 95% (mean, 3.5 min) and Bispectral Index version 1.1 (mean, 3.5 min). White *et al.*[15] used midlatency auditory evoked potentials to measure propofol drug effect, when administered as a continuous infusion (0.5 $mg \cdot kg^{-1} \cdot min^{-1}$), and calculated a k_{e0} of 3.5 min (mean value). All of these effect measures were modeled without including any delay in the electroencephalographic measure.

K_{e0} is dependent on the accuracy of the underlying pharmacokinetic model, and if the pharmacokinetic model is biased, the estimate of k_{e0} will biased by that error. One limitation of our study is that we did not include measurement of propofol plasma concentrations over time in our four groups. Similar to previously published work,[5,16–18] we applied the three-compartment model published by Schnider *et al.*[6] to predict the time course of the propofol plasma concentration. In the study by Doufas *et al.*,[5] the pharmacokinetic performance of the propofol pharmacokinetics reported by Schnider *et al.*[3] was validated with rapid arterial samples and found to be accurate. Because our study was designed specifically to test the hypothesis in the Doufas article that the difference in values of k_{e0} might depend on the difference between a bolus and a continuous infusion of propofol, we did not believe it was necessary to collect arterial blood samples in all patients during the bolus (similar to the infusion scheme used by Schnider in deriving the pharmacokinetics[6]) or the infusions (where the pharmacokinetics have been validated by both Doufas and Schnider).

However, the literature has not documented the accuracy of the Schnider pharmacokinetic model in the first minutes after bolus injection. Therefore, we added the bolus validation study and documented that neither model performed well in the first 3 min (fig. 4). The failure of both models in the first 3 min is an expected consequence of a flawed fundamental assumption with mammillary compartment models: instantaneous mixing in the central compartment. Conventional two- and three-compartment mammillary compartment models assume that drug added to the central compartment is instantaneously completely mixed, and that this mixed plasma instantaneously appears in the arterial circulation. This is not the case, as extensively reported by Henthorn *et al.*[19–21] and others.[22,23] The reason that more complex models have not been integrated into target-controlled infusion systems is that incorporating this into target-controlled infusion algorithms introduces considerable mathematical complexity. Because the problem with model misspecification is limited to the first few minutes after bolus injection, there is limited incentive to develop hybrid models to correct the fundamentally flawed assumption of instantaneous mixing.

The initial error in the pharmacokinetic models is evident for the full 5 min with the Marsh model but seems to be resolving by 3 min with the Schnider model. Therefore, the Schnider model comes closest to fitting the bolus validation data and would be the better of the two models to use for this purpose.

The simulation results from the bolus validation study (fig. 5) show that a $t_{½}$ k_{e0} of 2.0 min, coupled to a more accurate pharmacokinetic model, predicts a peak effect site concentration of 1.9 min, as observed with our bolus data (table 4). This is fairly close to the $t_{½}$ k_{e0} of 2.2 min that we estimated for the three infusion groups, and demonstrates that most of the difference in k_{e0} between bolus and infusion administration is an artifact caused by the inability of mammillary models to accurately describe the concentrations in the first few minutes after bolus injection. The actual rate of blood–brain equilibration may not differ between bolus and infusion methods of administration.

This does not preclude the possibility that there are

physiologic reasons the rate of plasma–effect site equilibration might change with infusion rate. Upton and Ludbrook[24,25] demonstrated that propofol decreases cerebral blood flow in a dose-dependent manner. This might explain why the plasma–effect site equilibration time of propofol could change between a bolus, whose high early concentrations acutely decrease cerebral blood flow, and an infusion, where the changes in cerebral blood flow would be small.

The rate of propofol administration influences the apparent rate of plasma–effect site equilibration. This is partly, and perhaps mostly, a result of the inability of conventional pharmacokinetic models to accurately describe the first few minutes after bolus injection. Target-controlled infusion devices need to select the value of k_{e0} that will most accurately represent the effect site concentrations over time. The error in the pharmacokinetic model with rapid administration can be partly compensated for by the selection of k_{e0}. If the maximum infusion rate is between 300 and 900 ml/h, this corresponds to the infusion rates in our three infusion groups, and the $t_{½}$ k_{e0} should be approximately 2.2 min (k_{e0} = 0.32). However, if the infusion is closer to our bolus rate (2.5 mg/kg over 10 s ≈ 6,300 ml/h), the faster $t_{½}$ k_{e0} of 1.2 min will better approximate the time course of drug effect. These values of k_{e0} are for use with the Schnider pharmacokinetics. If these data are to be implemented with other pharmacokinetics, then they should be implemented to achieve the predicted time of peak effect of 1.5 min if the device delivers an induction dose of propofol over a minute or less. If the pump is unable to infusion propofol that quickly, selecting k_{e0} based on a peak effect of 1.8 min is appropriate.[2]

We conclude that the observation of Doufas *et al.* is correct, although the explanation is surprising. There is a difference in the apparent rate of plasma–effect site equilibration between propofol boluses and propofol infusions. The difference is mostly caused by misspecification in the pharmacokinetic model over the first few minutes after bolus injection. A pharmacokinetic model that accurately predicted propofol concentration in the first few minutes after bolus injection, and for many hours after infusion, might improve the accuracy of target-controlled infusion administration when targeting the site of drug effect. If propofol infusion rate affects the apparent k_{e0} even when the pharmacokinetic model is unbiased, there may also be a physiologic basis for dependence of k_{e0} on propofol infusion rate.

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