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Induction Speed Is Not a Determinant of Propofol

Pharmacodynamics

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Abstract

Summary—We used individual pharmacodynamic modeling to demonstrate that different sedation endpoints occur at the same effect site propofol concentration, independent of the infusion rate of propofol.

Background—Evidence suggests that the rate at which they are infused may influence plasma-effect site equilibration of intravenous anesthetics. We used 5 different rates of propofol administration to test the hypothesis that different sedation endpoints occur at the same effect site propofol concentration, independent of the infusion rate. We concurrently evaluated the *automated responsiveness monitor* (ARM) against other sedation measures and the propofol effect site concentration.

Methods—With Human Studies Committee approval, 18 healthy volunteers received 5 consecutive target-controlled propofol infusions. During each infusion the effect site concentration was increased by a rate of 0.1, 0.3, 0.5, 0.7, or 0.9 $\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}$. Bispectral index and ARM were recorded at frequent intervals. The times of syringe drop and loss and recovery of responsiveness were noted. Pharmacokinetic and pharmacodynamic modeling was performed using NONMEM.

Results—Once the correct rate of plasma-effect site equilibration (k_{e0}) was determined for each individual ($k_{e0} = 0.17 \text{ min}^{-1}$, time-to-peak effect = 2.7 min), the effect site concentrations associated with each clinical measure were not affected by the rate of rise of effect site propofol concentration.

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ARM correlated with all clinical measures of drug effect. Subjects invariably stopped responding to ARM at lower effect site propofol concentrations than those associated with loss of responsiveness.

Conclusions—Population-based pharmacokinetics, combined with real-time electroencephalographic measures of drug effect, may provide a means to individualize pharmacodynamic modeling during target-controlled drug delivery. ARM appears useful as an automated measure of sedation and may provide the basis for automated monitoring and titration of sedation for a propofol delivery system.

Introduction

Although it is generally assumed that the rate of equilibration between the plasma and the site of drug effect is independent of the rate of drug administration, several studies suggest this may not be the case for intravenous anesthetics.^{1–4} There may be complex interactions among the rate, dose, and time of anesthetic induction^{5–7}, as well as physiological factors^{1,3,4,8–10}, which might influence the rate of plasma-effect site equilibration. If infusion rate alters the time course of plasma-effect site equilibration, this would be a new source of variability that must be understood when designing infusion regimes. We tested the hypothesis that different sedation endpoints occur at the same effect site propofol concentration, independent of the propofol infusion rate. This study was designed using a prototype sedation delivery system for propofol administration.

This study also examined the performance of an *automated responsiveness monitor* (ARM) (previously called the *automated responsiveness test* or “ART”), a novel feedback system for titration of sedative drugs.^{11,12} We have previously shown that patients stop responding to ARM during moderate sedation and that patients who are otherwise unresponsive invariably do not respond to ARM.^{11,12} Given the large variability in propofol effect site concentrations at loss of responsiveness, ARM may be a useful device to assess patient sensitivity to propofol during titration, particularly if ARM is integrated into a propofol delivery system. ARM has not been prospectively tested under non-steady state conditions, and thus, was included in this examination of the relationship of propofol infusion rate to measures of propofol drug effect.

Materials and Methods

With approval of the University of California at San Francisco Committee on Human Research (San Francisco, California) and written informed consent, we evaluated 18 healthy volunteers of both sexes. Age was restricted to 18–50 years. Volunteers fasted at least eight hours before the study.

Protocol

The sedation delivery system includes three major elements: 1) standard anesthetic monitoring including arterial pressure, electrocardiogram, end-tidal pCO₂, and oxygen saturation; 2) a computer-controlled propofol infusion system; and 3) the Automated Responsiveness Monitor (ARM). The Automated Responsiveness Monitor consists of an earphone positioned in one ear, held in place with a strap, and a handpiece about the size and shape of a small cellular phone strapped into the palm of the dominant hand. Earpiece function is monitored with an online indicator. A thumb button is mounted on the handpiece. A computerized voice asks the participant to press the button at regular intervals. A vibrator built into the hand piece vibrates at the same time. The voice and vibration repeat until the thumb button is pressed (maximum of five requests over a 10-second period). The voice gets louder and the vibrations get more intense with each repetition.

The sedation delivery system monitors and ARM apparatus were applied to the participating volunteers. Electrodes to capture the bispectral index of the electroencephalogram (BIS™ 3.3 algorithm) were applied to the forehead according to the manufacturer's instructions (Aspect Medical Systems, Inc., Newton, MA, USA). The BIS recording began with a 2 min period of quiet relaxation with the volunteer's eyes closed.

A 20-g venous catheter was inserted into the non-dominant arm above the wrist for the propofol infusion. A 20-g catheter was inserted at the antecubital fossa on the dominant arm and lactated Ringer's solution (200 ml) was infused as a bolus. Subsequently, fluid was infused at a rate of 100 ml/h. A 20-g catheter for blood sampling was inserted into the radial artery of the non-dominant hand. Surface warming was used to maintain tympanic membrane temperature between 37.0 and 37.5°C. Volunteers breathed 30% oxygen via a standard anesthesia mask during each trial.

The volunteers were familiarized with the ARM apparatus for 10–15 minutes before the first sedation trial. The volume of the earpiece was adjusted to a level that the volunteer was able to hear easily. We confirmed that the volunteers responded promptly to the ARM during this pre-study period.

We used a target-controlled drug delivery system according to the method of Shafer and Gregg¹³ to target propofol effect site concentrations using the propofol pharmacokinetics reported by Schnider et al.¹⁴ with a half-life of plasma-effect site equilibration of 91 s.¹⁵ The performance of the system was previously evaluated under pseudo-steady state conditions.¹⁶ The drug delivery system consisted of a Harvard 2 (Harvard Clinical Technology, South Natick, MA) electronic syringe pump and a customized software driver.

The software did not target steady-state effect site propofol concentrations, but instead produced a constant ramp in the effect site concentration. The effect site ramp rates were 0.1, 0.3, 0.5, 0.7, and 0.9 $\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}$. Each ramp began either at 0 (first ramp) or a predicted effect site concentration lower than 0.5 $\mu\text{g}/\text{ml}$. So as to eliminate any potential time- or pre-trial effect site concentration-related effects on the study outcomes, the order of the 5 sedation ramps was randomized within and across the volunteers.

Each ramp was continued until loss of responsiveness (LOR), as defined by an Observer's Assessment Alertness/Sedation (OAA/S) score equal to 1 (*i.e.*, no response to mild shaking).¹⁷ The OAA/S score was initially measured after the first negative response to the ARM prompt and was repeated every 15 sec thereafter, immediately after each ARM assessment (negative or positive). After LOR, the infusion was stopped, and OAA/S was determined every 15 seconds until recovery of responsiveness (OAA/S = 2).

Monitoring continued during the recovery period, for at least 15 minutes after the volunteers regained responsiveness. Once they had been awake for at least 15 minutes and their predicted propofol effect site concentrations had decreased below 0.5 $\mu\text{g}/\text{ml}$, the next ramp in the randomized sequence was started. Figure 1 shows a representative trial with the effect site (Fig. 1A) and plasma (Fig. 1B) propofol concentrations, as well as bispectral index over time (Fig. 1A) at propofol ramp rates of 0.9, 0.5, 0.7, 0.1, and 0.3 $\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}$.

Measurements

Heart rate, blood pressure, end-tidal pCO₂, respiratory rate, arterial oxygen saturation, and BIS values were recorded by an automated data-acquisition system for off-line analysis. End-tidal CO₂ was collected through a tight-fitting, hand-held anesthesia mask. The data were captured at 15-second intervals except for the non-invasive blood pressure measurement, which was captured at 2-minute intervals.

The first clinical end-point was the “syringe-drop.” With each ramp, the volunteer held a water-filled 60-ml syringe over the floor with the palm facing down. The time at which the subject released the syringe was recorded.

The second and third clinical end-points were loss and recovery of responsiveness, respectively, which were based upon the responsiveness component of the OAA/S.¹⁷ Loss and recovery of responsiveness were defined as the first OAA/S score of 1 (loss – no response to mild shaking) followed by the first OAA/S score of 2 (recovery – response to mild shaking).

Our fourth clinical endpoint was loss of the ability to respond to the ARM prompt. ARM was tested at 15-second intervals during each ramp, as well as during recovery from each propofol infusion.

Arterial blood samples for propofol determination were obtained at each of the four clinical endpoints. Additionally, blood samples were obtained at each 0.5 µg/ml predicted effect site propofol concentration increment during the 0.1, 0.3, and 0.5 µg·ml⁻¹·min⁻¹ ramp trials and at each 1.0 µg/ml during the 0.7 and 0.9 µg·ml⁻¹·min⁻¹ ramp trials. The samples were analyzed using high-performance liquid chromatography assay modified from the method of Plummer.¹⁸ This method has a detection limit of 5 µg/L and a coefficient variation of 4.1% at a propofol plasma level of 2 µg/ml.

Data Analysis

Individual demographic and morphometric data were presented in tabular format. Heart rate, non-invasive blood pressure, respiratory rate, end-tidal CO₂ and arterial oxygen saturation were averaged within and then across the volunteers and presented for each propofol infusion ramp rate separately.

We used the traditional two-step approach of Sheiner *et al.*¹⁹ to model individual subject effect site concentrations with the measured arterial propofol concentrations and the BIS as a continuous high-resolution measure of drug effect. With this model, pharmacokinetics of the drug are estimated, followed by an estimation of k_{e0} , the rate constant for plasma-effect site equilibration, and the parameters of the concentration vs. response model.

Pharmacokinetics—The parameters of a traditional three-compartment mammillary pharmacokinetic model were fit to the data using NONMEM²⁰ with first-order conditional estimation. The drug infusion regimen recorded by the sedation delivery system every 15 seconds was used as the input to the model. NONMEM estimated post-hoc Bayesian volumes and clearances in each individual, as well as typical values (e.g., geometric means) of the volumes and clearances. Variability in volume and clearance was modeled assuming log-normal inter-individual variability. Residual intra-individual error was assumed to be proportional to the prediction (*i.e.*, a constant coefficient of variation).

Goodness of fit was assessed by examination of plots of predicted vs. measured concentration and calculation of the median performance error and the median absolute performance error.

²¹ First, for each blood sample the performance error (PE) was calculated as:

$$PE = \frac{C_m - C_p}{C_p} * 100,$$

where C_m and C_p are the measured and predicted plasma propofol concentrations, respectively. Subsequently, the median performance errors (MDPE) and the median absolute performance errors (MDAPE) were calculated for each subject separately. Performance error, MDPE and MDAPE were calculated for each subject twice: first using the original prediction for plasma

propofol levels based on the pharmacokinetics reported by Schnider *et al.*¹⁴, and second using the prediction derived from the individual *post hoc* Bayesian estimates. The performance indices based upon the original and the post-hoc Bayesian estimates were compared using paired *t*-tests with a level of significance of $P < 0.05$.

The influence of time and ramp rate on propofol pharmacokinetics was assessed by plotting the measured/predicted propofol concentrations against time and ramp rate.

Pharmacodynamics—The *post hoc* Bayesian estimates of each volume and clearance term were used to calculate plasma and effect site concentrations. As described by Sheiner *et al.*,¹⁹ the effect site was assumed to be linked to the plasma by a compartment of trivial volume with a first-order equilibration constant of k_{e0} . The shape of the effect site concentration vs. BIS response relationship was assumed to be sigmoidal and described by the logistic relationship:

$$\text{BIS} = E_0 - E_{\max} \frac{C_e^{\gamma_{\text{BIS}}}}{C_{e_{50, \text{BIS}}}^{\gamma_{\text{BIS}}} + C_e^{\gamma_{\text{BIS}}}},$$

where E_0 is the baseline BIS, $E_{\max}$ is the maximum effect of propofol on BIS, C_e is the propofol concentration at the site of drug effect, and $C_{e_{50, \text{BIS}}}$ is the effect site propofol concentration associated with 50% of the maximum effect. γ_{BIS} is the steepness of the concentration vs. response relationship (also termed the “Hill coefficient”). The parameters k_{e0} , $C_{e_{50, \text{BIS}}}$, E_0 , $E_{\max}$, and γ_{BIS} were estimated using NONMEM. Inter-individual variability was permitted on k_{e0} and $C_{e_{50, \text{BIS}}}$, and was assumed to be log-normally distributed. Residual intra-individual error was assumed to be additive. T_{peak} was calculated by simulating an intravenous bolus injection and determining the time of peak concentration in the effect site.²²

The relationship between ramp rate and $C_{e_{50, \text{BIS}}}$ was modeled assuming a linear relationship between $C_{e_{50, \text{BIS}}}$ and ramp rate. Model selection was based on the improvement in $-2 \log$ likelihood, with a reduction in $-2 \log$ likelihood of 3.84 considered significant ($\chi^2 < 0.05$).

We assessed model performance by plotting the *post hoc* Bayesian BIS predictions against the measured BIS and looking for systematic misspecification. Inter-subject variability was displayed by plotting curves showing the individual effect site propofol concentration vs. BIS relationships.

The effect site propofol concentration at “syringe drop” was calculated using the *post hoc* Bayesian estimates of the volumes, clearances, and k_{e0} . The influence of ramp rate on the sedation delivery system and Bayesian prediction of the propofol effect site concentration was evaluated graphically by calculating the mean concentration and 95% confidence bounds at syringe drop at each ramp rate. The confidence bounds were constructed as $\pm 1.96 \text{ SEM}$.

The effect site propofol concentrations at loss of responsiveness (first failure to respond to mild shaking) and recovery of responsiveness (first response to mild shaking after loss of responsiveness) were calculated using the *post hoc* Bayesian estimates of the volumes, clearances, and k_{e0} . The influence of ramp rate on loss and recovery of responsiveness using the sedation delivery system and Bayesian prediction was evaluated graphically by calculating the mean concentration and confidence bounds at loss and recovery of responsiveness at each ramp rate. The confidence bounds were constructed as $\pm 1.96 \text{ SEM}$.

The relationship between the effect site propofol concentrations at loss and recovery of responsiveness was evaluated by plotting the concentration at loss of responsiveness vs. the

concentration at recovery of responsiveness vs. the line of identity. Similarly, the relationship between BIS at loss and recovery of responsiveness was evaluated by plotting the BIS at loss of responsiveness vs. BIS at recovery of responsiveness vs. the line of identity.

Automated Responsiveness Monitor (ARM)—Logistic regression was performed with NONMEM to estimate the probability of ARM response as a function of effect site propofol concentration. Each response to ARM was given a score of 1, and each non-response to ARM was given a score of 0. The probability of response to ARM was then calculated as:

$$P = 1 - \frac{Ce^{\gamma_{ARM}}}{Ce_{50, ARM}^{\gamma_{ARM}} + Ce^{\gamma_{ARM}}}$$

If, as defined above, R is the observed response to ARM and P is the probability of response to ARM, then the probability of each observation was defined as

$$\text{Probability of observation} = R \times P + (1 - R) \times (1 - P)$$

The probability of response is the probability that the patient will respond to the stimulus, ranging from 1 when no drug is present to 0 as the propofol concentration approaches infinity. The probability of an observation refers to an individual observation during the study. Since P in the model is the probability of response, then if the patient responded, the probability of that observation is P. However, if the patient did not respond, then the probability of that in the model is 1–P. For example, if no drug is present, then the probability of response is 1, and the probability of non-response is 0. The probability of the observation depends on what the observation was. NONMEM estimated the model parameters to identify the parameter values that maximized the probability of all of the observations.

We also used this model, *mutatis mutandis*, to estimate the Ce_{50} for syringe drop ($Ce_{50, \text{syringe}}$), loss of responsiveness ($Ce_{50, \text{LOR}}$), and recovery of responsiveness ($Ce_{50, \text{ROR}}$). We compared the $Ce_{50, \text{ARM}}$ against $Ce_{50, \text{BIS}}$, $Ce_{50, \text{syringe}}$, $Ce_{50, \text{LOR}}$, and $Ce_{50, \text{ROR}}$. We also assessed graphically the relationship between the lowest effect site propofol concentration at which each subject became unresponsive to ARM at any of the ramp rates and the average concentration at which “syringe drop,” loss and recovery of response to mild shaking occurred.

Results

Hemodynamic and respiratory physiology was essentially unchanged during the various infusion rates of propofol. Demographic data are shown in Table 1.

Pharmacokinetics—*Post hoc* Bayesian volumes and clearances as estimated by NONMEM for each individual separately are presented in Table 2. The *post hoc* Bayesian estimates of volumes and clearances improved the prediction of plasma propofol concentration compared with the original population pharmacokinetics (Table 3). Both pharmacokinetic predictions were unbiased (MDPE < 2%). The accuracy of the Schnider’s pharmacokinetic model was very good (MDAPE of 21%), but the accuracy was significantly greater for the *post hoc* Bayesian pharmacokinetic parameters (MDAPE of 13%; $P < 0.05$). Individual *post hoc* Bayesian estimates of the pharmacokinetic parameters improved the relation between the predicted and measured plasma propofol concentrations (Fig. 2B) compared to the original estimates (Fig. 2A).

Neither time (Fig. 3A and 3C) nor ramp rate (Fig. 3B and 3D) affected the residual errors, which suggested that neither of these covariates influenced the pharmacokinetics of propofol.

Pharmacodynamics—Individual pharmacodynamic results for the 18 volunteers are shown in Table 4. Intersubject variability could only be estimated on k_{e0} and $Ce_{50, BIS}$. NONMEM estimated that the BIS response started at 96 (E_0), and reached a nadir at 20 ($E_0 - E_{max}$). The k_{e0} estimated by NONMEM was $0.17 \text{ min}^{-1} \pm 30\%$ coefficient of variation (C.V.), which yielded a typical time to peak effect of 2.7 min. Plotting the *post hoc* Bayesian BIS predictions against the measured BIS did not reveal any major model misspecification (Fig. 4A); however, individual propofol concentration vs. BIS relationships demonstrated considerable inter-subject variability (Fig. 4B). Ramp rate was not a significant covariate of $Ce_{50, BIS}$.

The predicted effect site concentrations of propofol and BIS values at which syringe drop, loss of responsiveness (LOR), and recovery of responsive (ROC) occurred are given in figures 5–7, respectively. LOR occurred at 29 ± 6 (mean $\pm$ SD), 12 ± 3 , 8 ± 2 , 7 ± 2 , and 5 ± 1 minutes after the start of the propofol infusion at rates of 0.1, 0.3, 0.5, 0.7, and $0.9 \mu\text{g}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}$, respectively. The original sedation delivery system prediction of the propofol effect site concentration at “syringe drop” (Fig. 5A) and “loss of responsiveness” (Fig. 6A) endpoints increased linearly as a function of ramp rate, whereas BIS values at each endpoint were similar across the different ramp rates (Figs. 5C and 6C). *Post hoc* Bayesian estimation of the effect site concentration using individually predicted k_{e0} values demonstrated that the end points were reached at the same effect site propofol concentration at each ramp rate (Figs. 5B and 6B). Recovery of responsiveness occurred at the same effect site propofol concentration independent of the ramp rate or the prediction model used (Figs. 7A, B, and C). This was an expected result because the plasma and effect site concentrations were changing more slowly on recovery of responsiveness and thus were in close equilibration and insensitive to errors in k_{e0} .

Prediction of the propofol effect site concentration, using the individual Bayesian estimates of the pharmacokinetic parameters and k_{e0} , showed very tight correlation between loss and recovery of responsiveness (Fig. 8A). This was not the case for the BIS values at loss and recovery of responsiveness (Fig. 8B), reflecting the intrinsic noise of the BIS measurement.

Automated Responsiveness Monitor (ARM)—Independent of the infusion rate, at low propofol concentrations all the volunteers were able to respond to the ARM prompt, whereas at high concentrations none of them was able to do so (Fig. 9A). In between these is a concentration range where response to ARM was variable. This behavior is captured by the logistic regression model (Fig. 9B) that shows the transition from 100% probability of response to the ARM to 100% probability of no response to the ARM.

The effect site concentration at first loss of the ARM ($1.49 \pm 0.46 \mu\text{g}/\text{ml}$, mean $\pm$ SD) closely correlated with loss or recovery of responsiveness ($R^2=0.87$). This concentration (Fig. 10, thick line) is close to the concentration at which subjects dropped the syringe (Fig. 10, open circles) and was consistently below the concentration at which they lost responsiveness (Fig. 10, thin line) or regained responsiveness (Fig. 10, filled circles). The $Ce_{50, ARM}$ was $1.76 \pm 0.60 \mu\text{g}/\text{ml}$, which is 32% less than the $Ce_{50, LOR}$, $2.57 \pm 0.91 \mu\text{g}/\text{ml}$. The individual Ce_{50} values for loss of response to ARM closely correlated with $Ce_{50, BIS}$ ($R^2=0.73$), $Ce_{50, syringe}$, ($R^2=0.63$), $Ce_{50, LOR}$ ($R^2=0.91$), and $Ce_{50, ROR}$ ($R^2=0.88$).

Discussion

The main purpose of the study was to determine whether the responses to various clinical measures of sedation are influenced by the rate of rise of propofol effect site concentration. In

addition, we specifically assessed Automated Responsiveness Measure (ARM) against several clinical measures of sedation.

In order to test our first hypothesis, we modeled the effect site propofol concentration, using the two-step approach proposed by Sheiner *et al.*¹⁹ Initially, it appeared that the rate of rise of propofol's effect site concentration influenced both ARM and the other measures of sedation (Figs. 5 and 6, top graphs). This was based on the integrated pharmacokinetic/pharmacodynamic model of propofol reported by Schnider *et al.*^{14,15} However, we were able to use the bispectral index to revise the pharmacokinetic and pharmacodynamic model for each subject. Based on the *post hoc* Bayesian pharmacokinetics and individualized values of k_{e0} , we found that the effect site propofol concentration for the clinical measures of drug effect was independent of the rate of rise of the effect site propofol concentration.

Given that the pharmacokinetics reported by Schnider *et al.*^{14,15} performed well in this study and that BIS was available to the computer throughout the study, these results suggested that real-time estimation of k_{e0} using model prediction of pharmacokinetics and electroencephalographic measure of drug effect may be a viable way to individualize target controlled infusions that target the site of drug effect.

We are unable to explain the discrepancy between the value of k_{e0} (0.17 min^{-1}) and t_{peak} (2.7 min) in this study and the k_{e0} (0.46 min^{-1}) and t_{peak} (1.7 min) reported by Schnider *et al.*¹⁵ and validated by Struys *et al.*²³ The pharmacokinetics reported by Schnider *et al.*¹⁴ performed well in this study, so the basis of the discrepancy was entirely with the electroencephalographic hysteresis. One possibility is that the hysteresis was affected by the mode of administration. While Schnider *et al.*²³ performed both bolus and an infusion studies, it is likely that most of the information about plasma-effect site equilibration delay came from the bolus data. In contrast, the present study was entirely based on infusions and even the most rapid effect site ramp rate still required 5 minutes to achieve unresponsiveness. It may be that plasma effect site propofol equilibration varies between boluses (e.g., very rapid infusions [2.5 mg/kg over 20 seconds]) and more conventional infusions. This is a readily testable hypothesis. It might also be affected by the time delay in the BIS monitor (about 15 seconds), which we did not include in the model. Schnider *et al.*, have centered the electroencephalographic epoch on the time point of the observation. We did not do this, and it could have modestly affected our estimates.

Early distribution kinetics determined the rate and extent of drug distribution to the brain and other tissues.²⁴ Conventional pharmacokinetic models may overestimate the central volume of distribution because the complexity of intravascular mixing is ignored²⁵ and thus the estimate of central volume of distribution is very dependent on the details of early drug sampling. If a standard mammillary pharmacokinetic model is to be used by a target controlled infusion system (and such models are the only ones presently incorporated in such systems), then the ideal pharmacokinetic profile should be derived from data obtained during and after a brief drug infusion.²⁶ This is consistent with the observation that the most accurate results are with target controlled infusion devices using pharmacokinetic data sets derived from "slow injection" or "continuous infusion" studies.²⁷⁻²⁹ However, both the Schnider pharmacokinetic study¹⁴ and the present study are based on infusions and rapid arterial sampling; thus, differences in study design can't explain the differences in estimates of k_{e0} .

Ludbrook *et al.* demonstrated that propofol decreases local cerebral blood flow in sheep³⁰ and humans¹⁰ in a concentration-dependent manner. This might explain why the k_{e0} of propofol could change between a bolus, which might acutely decrease cerebral blood flow, and an infusion, where the changes in cerebral blood flow would be attenuated by the lower peak arterial concentration.

Lastly, Kuizenga *et al.* demonstrated that the addition of a second effect site improves the prediction of the EEG response to a propofol infusion.³¹ Interestingly, k_{e0} estimated with parametric and nonparametric modeling of EEG^{31,32} and BIS data³² was almost identical ($0.16\text{--}0.21\text{min}^{-1}$) to ours, while the median time to loss of responsiveness was 2.8 minutes.³¹

Interestingly, loss of response to the Automated Responsiveness Monitor (ARM) occurred at approximately the same concentration as a subject's releasing a filled syringe and reproducibly occurred at a effect site propofol concentrations 15–40% less than those associated with loss of responsiveness (Fig. 10), providing a degree of protection from excessive sedation. Automated Responsiveness Monitor correlates well with other clinical measures of sedation, as well as with effect site propofol concentration. The effect site propofol concentration at which subjects lost response to ARM was independent of the rate of rise of concentrations over the range studied, provided that the correct rate of plasma-effect site equilibration was used.

In conclusion, it may be possible to estimate individual k_{e0} values from population estimates of pharmacokinetic parameters and real-time measurements of electroencephalographic effect, and thus optimize the pharmacokinetic/pharmacodynamic model in target-controlled infusion systems. For the range of infusions studied, the rate of rise in the effect site concentration does not affect propofol pharmacodynamics. Future studies need to address whether propofol's rate of blood-brain equilibration is faster following bolus administration than following conventional infusions. Automated responsiveness appears useful as a measure of sedative drug effect.

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Figure 1.

A representative volunteer trial. Graph A shows the propofol effect site concentration and bispectral index during 5 consecutive ramps (0.9, 0.5, 0.7, 0.1, and 0.3 $\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}$). Graph B shows the predicted (solid line) and the measured (circles) arterial propofol concentrations.

Figure 2.

Goodness of fit for the original predictions (graph A) and the predictions based on the post-hoc Bayesian estimates (graph B) vs. the measured arterial propofol concentrations.

Figure 3.

The influence of time (graphs A and C) and ramp rate (graphs B and D) on the measured/predicted propofol concentrations. Graphs A and B present the predictions from the original pharmacokinetic model,¹⁴ and graphs C and D are the predictions from the post-hoc Bayesian model.

Figure 4.

The goodness of fit for the pharmacodynamic model based on BIS (graph A); Fig. 4B shows the inter-individual variability in the pharmacodynamic model.

Figure 5.

The relationship of the effect site concentration and BIS at the time of syringe drop to the effect site ramp rate. With the wrong rate constant (k_{e0}) (graph A), it appeared that at higher ramp rates more propofol was required at the effect site to induce syringe drop. However, when the individualized values of k_{e0} were used, the effect site concentration associated with syringe drop was independent of the rate of rise of the effect site propofol concentration (graph B). This was consistent with the BIS results (graph C) showing that the BIS at the time of syringe drop appeared to be independent of the rate of rise of effect site propofol concentration.

Figure 6.

Similar to Figure 5, the effect site propofol concentration associated with loss of responsiveness (graph A) appeared to increase with increasing ramp rates. However, when the value of the rate constant (k_{e0}) was individualized, the effect site propofol concentration was independent of the ramp rate (graph B); this was also true for the BIS (graph C).

Figure 7.

The effect site propofol concentration associated with recovery of responsiveness was independent of the rate constant (k_{e0}), whether determined with the original (graph A) or individualized values of k_{e0} (graph B), likely reflecting the slow rate of change of both plasma and effect site concentrations and hence near-equilibration between them at the time of recovery of responsiveness. As with times to syringe drop and loss of responsiveness, BIS at recovery of responsiveness appeared to be independent of the rate of rise of effect site propofol concentration (graph C).

Figure 8.

The effect site concentrations at loss of responsiveness were nearly identical to those at recovery of responsiveness (graph A). There was less agreement between the bispectral index values on loss of responsiveness and recovery of responsiveness (graph B).

Figure 9.

Graph A shows every recording of the automated responsiveness monitor (ARM) in every subject. Each horizontal line represents a single subject and the ticks show individual ARM responses. The presence (response) and lack (no response) of ARM response, as a function of the effect site propofol concentration (X axis, graph B), are indicated by ticks above and below the line, respectively. Graph B shows the inter-individual variability in ARM response.

Figure 10.

The propofol effect site concentrations at the first loss of the automated responsiveness monitor (ARM, thick line), "syringe drop" (open circles), loss of responsiveness (thin line), and recovery of responsiveness (filled circles) in each individual.

Table 1

Demographics of the subjects

Volunteers	Gender	Age (yr)	Weight (Kg)	Height (m)
1	F	27	80.5	1.65
2	F	26	65.9	1.65
3	M	32	80.5	1.80
4	M	24	83.3	1.80
5	M	30	65.3	1.78
6	F	23	60.4	1.60
7	F	43	55.0	1.65
8	F	24	57.7	1.61
9	F	25	59.1	1.63
10	F	30	59.1	1.75
11	F	23	50.9	1.63
12	M	29	73.6	1.70
13	F	43	69.5	1.68
14	F	20	75.5	1.72
15	F	36	55.9	1.65
16	M	24	71.4	1.80
17	F	22	66.8	1.63
18	M	35	82.3	1.83
Median		27	66.4	1.67
Min		20	50.9	1.60
Max		43	83.3	1.83

Table 2

Pharmacokinetic parameters in individual subjects.

Volunteers	V ₁	V ₂	V ₃	Cl ₁	Cl ₂	Cl ₃
1	5.6	6.8	142	2.5	1.1	1.0
2	7.5	8.4	142	3.0	1.1	2.4
3	9.0	6.8	142	2.8	1.1	1.3
4	8.3	7.4	142	2.6	1.1	1.4
5	6.4	9.1	142	2.6	1.1	1.7
6	5.6	8.6	142	1.6	1.1	1.6
7	6.8	6.0	142	2.0	1.1	1.4
8	4.9	7.8	142	1.7	1.1	1.4
9	7.3	6.9	142	2.7	1.1	1.2
10	5.4	6.1	142	2.0	1.1	1.3
11	5.3	6.1	142	1.6	1.1	1.5
12	5.5	9.6	142	2.2	1.1	1.4
13	5.9	7.9	142	2.6	1.1	1.8
14	5.3	8.7	142	3.1	1.1	1.7
15	5.5	6.6	142	1.8	1.1	1.2
16	6.3	6.2	142	1.6	1.1	1.6
17	3.7	6.5	142	2.2	1.1	1.1
18	3.2	3.5	142	1.4	1.1	0.8
Median	5.6	6.9	142	2.2	1.1	1.4
Typical Value	3.3	7.6	142	2.2	1.1	1.6
CV	0.6	0.5	na	0.3	na	0.4

V = volume; CI = clearance ; CV = coefficient of variation

Table 3
Performance Characteristics of the target controlled infusion.

Volunteers	Original		<i>Post Hoc</i> Bayesian	
	MDPE	MDAPE	MDPE	MDAPE
1	6.40	22.65	-0.96	18.28
2	-33.53	37.63	-7.51	22.31
3	-13.99	21.23	-2.97	22.40
4	-8.81	16.17	0.50	12.25
5	-14.42	14.69	-0.20	12.91
6	7.12	12.44	8.41	16.95
7	-8.28	13.72	-0.04	12.56
8	7.52	11.11	2.13	9.12
9	-18.92	22.59	0.08	13.26
10	5.26	20.00	0.62	18.29
11	15.50	23.22	1.70	14.04
12	-1.49	11.06	-0.12	11.02
13	-20.23	20.23	-2.70	11.83
14	-21.50	21.50	-2.04	9.57
15	11.71	21.11	5.13	18.35
16	20.95	32.62	1.88	18.06
17	4.98	15.99	1.50	11.34
18	74.16	74.16	8.45	12.30
Median	1.75	20.67	0.29	13.09

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

Table 4

Pharmacodynamic results in individual subjects.

Volunteers	k_{e0} (min^{-1})	$C_{e50 \text{ BIS}}$ ($\mu\text{g}/\text{ml}$)	γ_{BIS}	E_0	E_{max}	$T_{1/2}k_{e0}$ (min)	t_{peak} (min)
1							
2	0.17	2.1	3.1	96	76	4.0	2.4
3	0.24	1.9	3.1	96	76	2.9	2.8
4	0.15	1.7	3.1	96	76	4.5	3.2
5	0.15	2.9	3.1	96	76	4.6	2.7
6	0.18	2.8	3.1	96	76	3.9	2.7
7	0.22	3.4	3.1	96	76	3.2	2.7
8	0.08	1.7	3.1	96	76	8.3	3.6
9	0.11	1.8	3.1	96	76	6.2	3.6
10	0.18	1.9	3.1	96	76	3.8	2.6
11	0.18	1.8	3.1	96	76	3.9	2.7
12	0.22	3.3	3.1	96	76	3.1	2.2
13	0.20	2.2	3.1	96	76	3.4	2.2
14	0.11	2.1	3.1	96	76	6.5	2.5
15	0.19	1.8	3.1	96	76	3.7	2.7
16	0.18	3.3	3.1	96	76	3.8	2.9
17	0.11	4.5	3.1	96	76	6.4	2.5
18	0.18	4.0	3.1	96	76	3.8	2.5
Median	0.18	2.1	3.1	96	76	3.8	2.7
Typical Value	0.17	2.4	3.1	96	76	4.2	na
CV	30%	30%					

 k_{e0} = rate constant for plasma-effect site equilibration $C_{e50 \text{ BIS}}$ = effect site propofol concentration associated with 50% of the maximum effect γ_{BIS} = steepness of the concentration vs. response relationship (Hill coefficient) E_0 = baseline BIS E_{max} = maximum effect of propofol on BIS $t_{1/2}k_{e0}$ = half-life of plasma-effect site equilibration T_{peak} = time to peak concentration at effect site