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Induction Speed Is Not a Determinant of Propofol Pharmacodynamics

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Background: **Evidence suggests that the rate at which intravenous anesthetics are infused may influence their plasma–effect site equilibration. The authors used five 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. The authors 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 five 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 $\mu g \cdot ml^{-1} \cdot min^{-1}$. The 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: **When the correct rate of plasma–effect site equilibration was determined for each individual (plasma–effect site equilibration = 0.17 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 increase of effect site propofol concentration. 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 seems useful as an automated measure of sedation and may provide the basis for automated monitoring and titration of sedation for a propofol delivery system.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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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 that 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 physiologic 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 regimens. 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*), 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 therefore was included in this examination of the relation 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 yr. Volunteers fasted for at least 8 h before the study.

Protocol

The prototype sedation delivery system includes three major elements: (1) standard anesthetic monitoring, in-

cluding arterial pressure, electrocardiogram, end-tidal partial pressure of carbon dioxide (P_{CO_2}), and oxygen saturation; (2) a computer-controlled propofol infusion system; and (3) the ARM. The ARM consists of an earphone positioned in one ear, held in place with a strap, and a handpiece approximately 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 handpiece vibrates at the same time. The voice and vibration repeat until the thumb button is pressed (maximum of five requests over a 10-s 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 (BIS) of the electroencephalogram (BIS® 3.3 algorithm; Aspect Medical Systems, Inc., Newton, MA) were applied to the forehead according to the manufacturer's instructions. The BIS recording began with a 2-min period of quiet relaxation with the volunteer's eyes closed.

A 20-gauge venous catheter was inserted into the nondominant arm above the wrist for the propofol infusion. A 20-gauge 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-gauge catheter for blood sampling was inserted into the radial artery of the nondominant 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 min 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 prestudy period.

We used a target-controlled drug delivery system according to the method of Shafer and Gregg[13] 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 $\mu g \cdot ml^{-1} \cdot min^{-1}$. Each ramp began either at 0 (first ramp) or at a predicted effect site concentration lower than 0.5 μg/ml. To eliminate any potential time- or pretrial effect site concentration–related effects on the study outcomes, the order of the five sedation ramps was randomized within and across the volunteers.

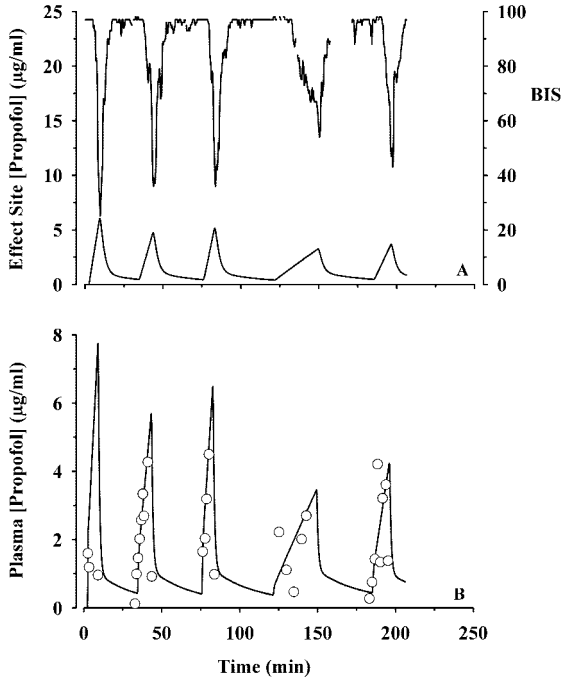

Fig. 1. A representative volunteer trial. (*A*) Propofol effect site concentration and Bispectral Index (BIS) during five consecutive ramps (0.9, 0.5, 0.7, 0.1, and 0.3 $\mu g \cdot ml^{-1} \cdot min^{-1}$). (*B*) Predicted (*solid line*) and measured (*circles*) arterial propofol concentrations.

Each ramp was continued until loss of responsiveness 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 s thereafter, immediately after each ARM assessment (negative or positive). After loss of responsiveness, the infusion was stopped, and the OAA/S score was determined every 15 s until recovery of responsiveness (OAA/S = 2).

Monitoring continued during the recovery period, for at least 15 min after the volunteers regained responsiveness. When they had been awake for at least 15 min and their predicted propofol effect site concentrations had decreased below 0.5 μg/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 the BIS over time (fig. 1A) at propofol ramp rates of 0.9, 0.5, 0.7, 0.1, and 0.3 $\mu g \cdot ml^{-1} \cdot min^{-1}$.

Measurements

Heart rate, blood pressure, end-tidal P_{CO_2}, respiratory rate, arterial oxygen saturation, and BIS values were

recorded by an automated data-acquisition system for off-line analysis. End-tidal carbon dioxide was collected through a tight-fitting, handheld anesthesia mask. The data were captured at 15-s intervals except for the noninvasive blood pressure measurement, which was captured at 2-min intervals.

The first clinical endpoint 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 endpoints were loss and recovery of responsiveness, respectively, which were based on 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-s 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. In addition, 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-$\mu g \cdot ml^{-1} \cdot min^{-1}$ ramp trials and at each 1.0 μg/ml during the 0.7- and 0.9-$\mu g \cdot ml^{-1} \cdot min^{-1}$ 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, noninvasive blood pressure, respiratory rate, end-tidal carbon dioxide, 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 the rate constant for plasma–effect site equilibration (k_{e0}) and the parameters of the concentration-*versus*-response model.

Pharmacokinetics

The parameters of a traditional three-compartment mammillary pharmacokinetic model were fit to the data using NONMEM[20] with first-order conditional estimation. The drug infusion regimen recorded by the sedation delivery system every 15 s 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 interindividual variability. Residual intraindividual 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-*versus*-measured concentration and calculation of the median performance error (MDPE) and the median absolute performance error (MDAPE).[21] First, for each blood sample, the performance error (PE) was calculated as

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

where C_m and C_p are the measured and predicted plasma propofol concentrations, respectively. Subsequently, the MDPEs and the MDAPEs 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 concentrations 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 on 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–*versus*–BIS response relation was assumed to be sigmoidal and described by the logistic relation

$$BIS = E_0 - E_{max}\frac{Ce^{\gamma_{BIS}}}{Ce_{50,BIS}^{\gamma_{BIS}} + Ce^{\gamma_{BIS}}},$$

where E_0 is the baseline BIS, E_{max} is the maximum effect of propofol on BIS, Ce is the propofol concentration at the site of drug effect, and $Ce_{50,\ BIS}$ is the effect site propofol concentration associated with 50% of the maximum effect. γ_{BIS} is the steepness of the concentration-*versus*-response relation (also termed the *Hill coefficient*). The parameters k_{e0}, $Ce_{50,\ BIS}$, E_0, E_{max}, and γ_{BIS} were estimated using NONMEM. Interindividual variabil-

ity was permitted on k_{e0} and Ce_{50} and was assumed to be log-normally distributed. Residual intraindividual 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 relation between ramp rate and $Ce_{50,\ BIS}$ was modeled assuming a linear relation between $Ce_{50,\ BIS}$ 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 square < 0.05).

We assessed model performance by plotting the *post hoc* Bayesian BIS predictions against the measured BIS and looking for systematic misspecification. Intersubject variability was displayed by plotting curves showing the individual effect site propofol concentration–*versus*–BIS relations.

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 ± 1.96 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 ± 1.96 SEM.

The relation between the effect site propofol concentrations at loss and recovery of responsiveness was evaluated by plotting the concentration at loss of responsiveness *versus* the concentration at recovery of responsiveness *versus* the line of identity. Similarly, the relation between BIS at loss and recovery of responsiveness was evaluated by plotting the BIS at loss of responsiveness *versus* BIS at recovery of responsiveness *versus* 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 nonresponse 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, 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. Because P in the model is the probability of response, if the patient responded, the probability of that observation is P. However, if the patient did not respond, the probability of that in the model is $1 - P$. For example, if no drug is present, the probability of response is 1, and the probability of nonresponse 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 ($Ce_{50,\ syringe}$), loss of responsiveness ($Ce_{50,\ LOR}$), and recovery of responsiveness ($Ce_{50,\ ROR}$). We compared $Ce_{50,\ ARM}$ against $Ce_{50,\ BIS}$, $Ce_{50,\ syringe}$, $Ce_{50,\ LOR}$, and $Ce_{50,\ ROR}$. We also assessed graphically the relation 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 and 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 pharmacokinetic model of Schnider *et al.*[14] 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 with the original estimates (fig. 2A).

Neither time (figs. 3A and C) nor ramp rate (figs. 3B and D) affected the residual errors, which suggested that

Table 1. Demographics of the Subjects

Volunteer No.	Sex	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

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 min^{-1} ± 30% coefficient of variation, 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–*versus*–BIS relations demonstrated considerable intersubject 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, and recovery of responsiveness occurred are given in figures 5, 6, and 7, respectively. Loss of responsiveness occurred at 29 ± 6 (mean ± SD), 12 ± 3, 8 ± 2, 7 ±

Table 3. Performance Characteristics of the Target-controlled Infusion

	Original		*Post Hoc* Bayesian	
Volunteer No.	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

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

Table 2. Pharmacokinetic Parameters in Individual Subjects

Volunteer No.	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

Cl = clearance; CV = coefficient of variation; NA = not applicable; V = volume.

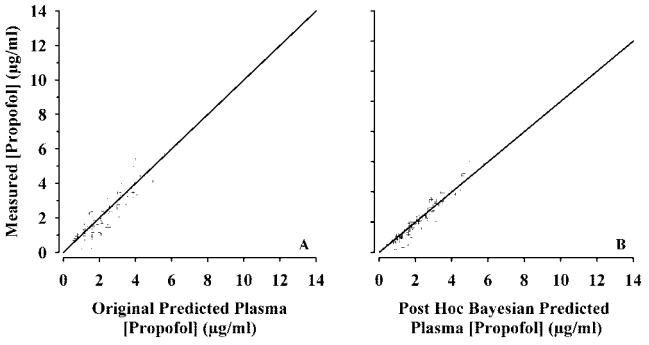

Fig. 2. Goodness of fit for the original predictions (*A*) and the predictions based on the *post hoc* Bayesian estimates (*B*) *versus* measured arterial propofol concentrations.

2, and 5 ± 1 min after the start of the propofol infusion at rates of 0.1, 0.3, 0.5, 0.7, and 0.9 $\mu g \cdot ml^{-1} \cdot min^{-1}$, respectively. The original sedation delivery system prediction of the propofol effect site concentration at the 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 endpoints 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–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 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.

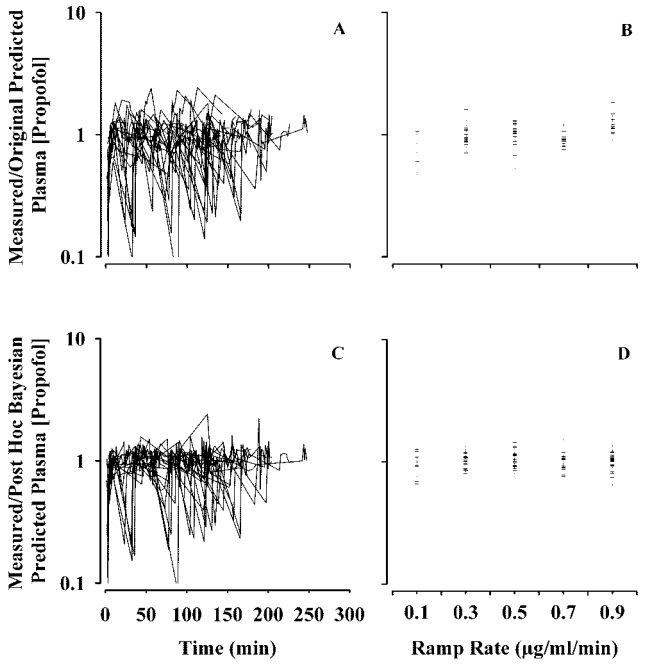

Fig. 3. Influence of time (*A* and *C*) and ramp rate (*B* and *D*) on the measured/predicted propofol concentrations. *A* and *B* present the predictions from the original pharmacokinetic model, and *C* and *D* are the predictions from the *post hoc* Bayesian model.

Automated Responsiveness Monitor

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). 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 ± 0.46 μg/ml, mean ± SD) was 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 ± 0.60 μg/ml, which is 32% less than the $Ce_{50\ LOR}$, 2.57 ± 0.91 μg/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 increase of propofol effect site concentration. In addition, we specifically assessed the ARM against several clinical measures of sedation.

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 seemed that the rate of increase of the effect site concentration of propofol influenced both the ARM and the other measures of sedation (figs. 5A and 6A). 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 BIS to revise the pharmacokinetic and pharmacodynamic model for each subject. Based on the *post hoc* Bayesian pharmacokinetics and individual-

Table 4. Pharmacodynamic Results in Individual Subjects

Volunteer No.	k_{e0}, min^{-1}	$Ce_{50,BIS}$, μg/ml	γ_{BIS}	E_0	E_{max}	$t_{1/2}k_{e0}$, min	t_{peak}, min
1	0.25	2.5	3.1	96	76	2.8	2.2
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%					

$Ce_{50,BIS}$ = effect site propofol concentration associated with 50% of maximum effect; CV = coefficient of variation; E_0 = baseline BIS; E_{max} = maximum effect of propofol on BIS; γ_{BIS} = steepness of the concentration-*vs.*-response relation (Hill coefficient); k_{e0} = rate constant for plasma–effect site equilibration; $t_{1/2}k_{e0}$ = half-life of plasma–effect site equilibration; t_{peak} = time to peak concentration at effect site.

ized 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 increase 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.

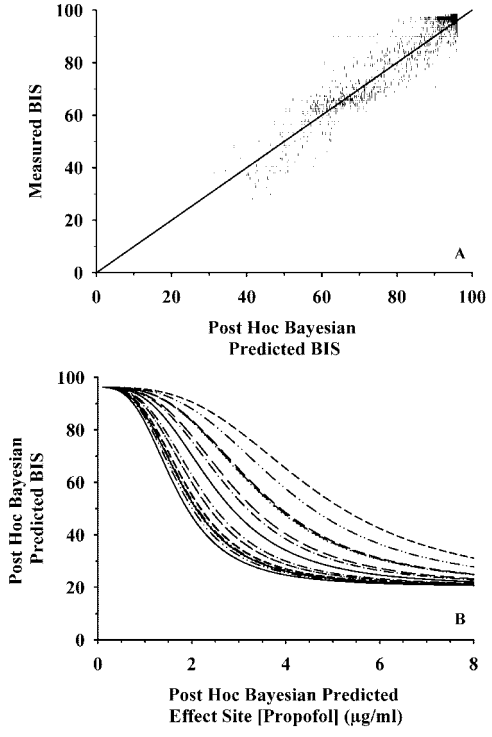

Fig. 4. (*A*) Goodness of fit for the pharmacodynamic model based on the Bispectral Index (BIS). (*B*) Interindividual variability in the pharmacodynamic model.

We are unable to explain the discrepancy between the values 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. Although Schnider *et al.*[15] 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 current study was entirely based on infusions, and even the most rapid effect site ramp rate still required 5 min 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 s]) and more conventional infusions. This is a readily testable hypothesis. It might also be affected by the time delay in the BIS® monitor (approximately 15 s), 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]

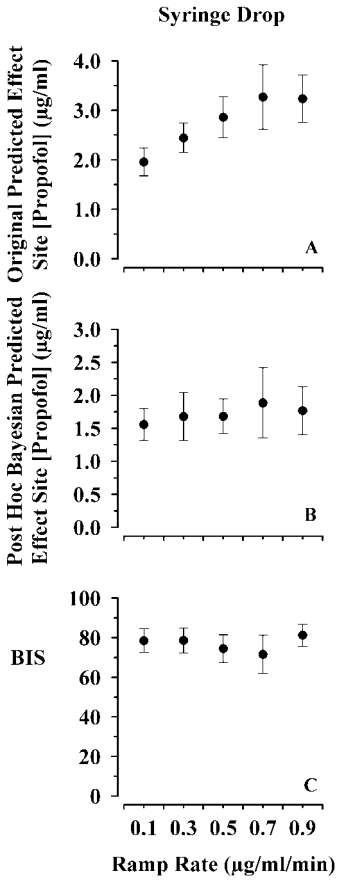

Fig. 5. Relation of the effect site concentration and the Bispectral Index (BIS) at the time of syringe drop to the effect site ramp rate. With the wrong rate constant (*A*), it seemed that at higher ramp rates, more propofol was required at the effect site to induce syringe drop. However, when the individualized rate constant values were used, the effect site concentration associated with syringe drop was independent of the rate of increase of the effect site propofol concentration (*B*). This was consistent with the BIS results (*C*) showing that the BIS at the time of syringe drop seemed to be independent of the rate of increase of effect site propofol concentration.

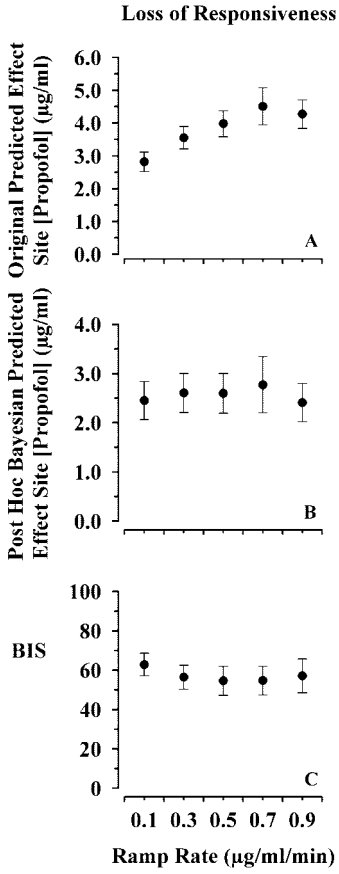

Fig. 6. Similar to figure 5, the effect site propofol concentration associated with loss of responsiveness (*A*) seemed to increase with increasing ramp rates. However, when the value of the rate constant was individualized, the effect site propofol concentration was independent of the ramp rate (*B*); this was also true for the Bispectral Index (BIS) (*C*).

Conventional pharmacokinetic models may overestimate the central volume of distribution because the complexity of intravascular mixing is ignored[25] and thus the estimate of central volume of distribution is 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), 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 pharmacokinetic study of Schnider *et al.*[14] and the current study are based on infusions and rapid arterial sampling; thus, differences in study design cannot explain the differences in estimates of k_{e0}.

Ludbrook *et al.*[10,30] demonstrated that propofol decreases local cerebral blood flow in humans and sheep 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.*[31] demonstrated that the addition of a second effect site improves the prediction of the electroencephalographic response to a propofol infusion. Interestingly, k_{e0} estimated with parametric and nonparametric modeling of electroencephalographic[31,32] and BIS data[32] was almost identical (0.16–0.21 min^{-1}) to ours, whereas the median time to loss of responsiveness was 2.8 min.[31]

Interestingly, loss of response to the ARM occurred at approximately the same concentration as a subject's releasing a filled syringe and reproducibly occurred at effect site propofol concentrations 15–40% less than those associated with loss of responsiveness (fig. 10), providing a degree of protection from excessive seda-

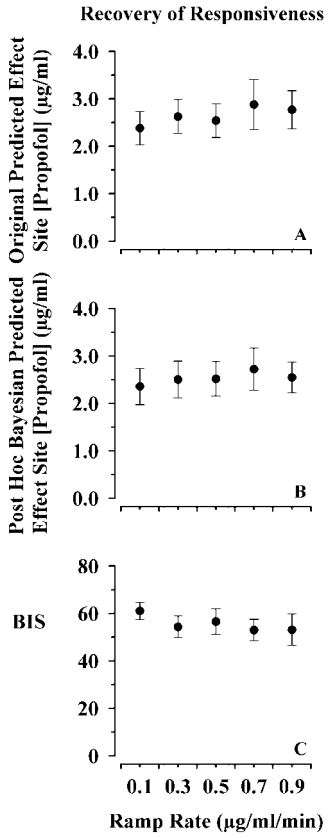

Fig. 7. The effect site propofol concentration associated with recovery of responsiveness was independent of the rate constant, whether determined with the original (*A*) or individualized values of the rate constant (*B*), likely reflecting the slow rate of change of both plasma and effect site concentrations and hence near equilibration between them at the time of recovery of responsiveness. As with times to syringe drop and loss of responsiveness, the Bispectral Index (BIS) at recovery of responsiveness seemed to be independent of the rate of increase of effect site propofol concentration (*C*).

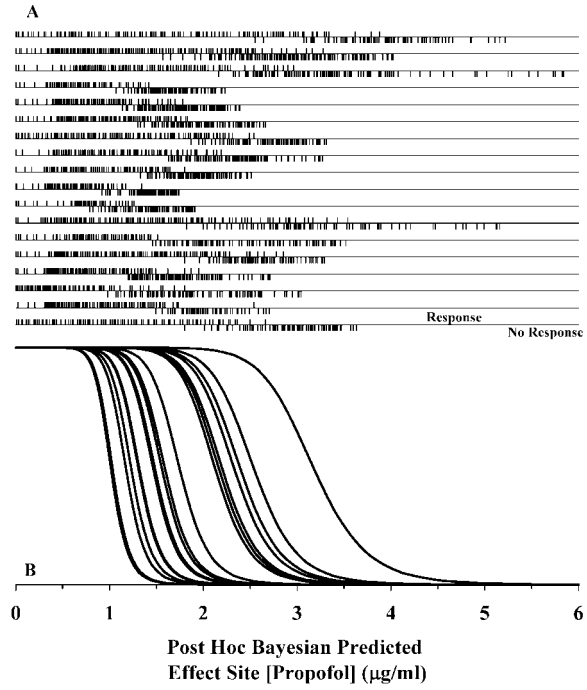

Fig. 9. (*A*) Every recording of the automated responsiveness monitor in every subject. Each *horizontal line* represents a single subject, and the *tick marks* show individual automated responsiveness monitor responses. The presence (response) and lack (no response) of automated responsiveness monitor response, as a function of the effect site propofol concentration (x-axis, *B*), are indicated by ticks above and below the line, respectively. (*B*) Interindividual variability in automated responsiveness monitor response.

tion. The ARM 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 the ARM was independent of the rate of increase 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 increase in the effect site concentration does not affect propofol pharmacodynamics. Future studies must

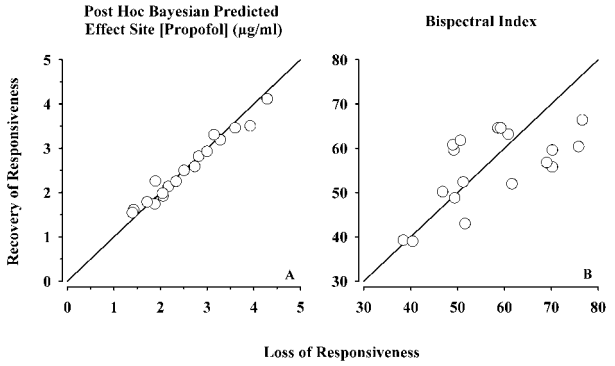

Fig. 8. Effect site concentrations at loss of responsiveness were nearly identical to those at recovery of responsiveness (*A*). There was less agreement between the Bispectral Index values on loss of responsiveness and recovery of responsiveness (*B*).

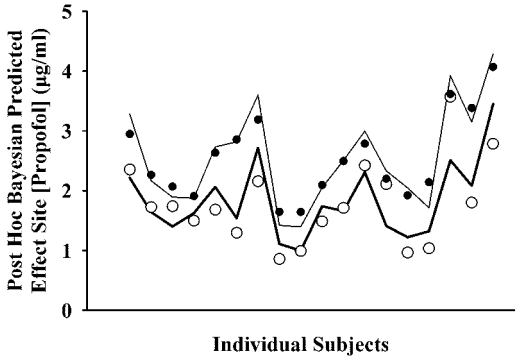

Fig. 10. Propofol effect site concentrations at the first loss of the automated responsiveness monitor (*thick line*), syringe drop (*open circles*), loss of responsiveness (*thin line*), and recovery of responsiveness (*filled circles*) in each individual.

address whether the rate of blood–brain equilibration of propofol is faster after bolus administration than after conventional infusions. Automated responsiveness seems useful as a measure of sedative drug effect.

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References

1. Upton RN, Ludbrook GL: A model of the kinetics and dynamics of induction of anaesthesia in sheep: Variable estimation for thiopental and comparison with propofol. Br J Anaesth 1999; 82:890–9
2. Stokes DN, Hutton P: Rate-dependent induction phenomena with propofol: Implications for the relative potency of intravenous anesthetics. Anesth Analg 1991; 72:578–83
3. Rolly G, Versichelen L, Huyghe L, Mungroop H: Effect of speed of injection on induction of anaesthesia using propofol. Br J Anaesth 1985; 57:743–6
4. Peacock JE, Lewis RP, Reilly CS, Nimmo WS: Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. Br J Anaesth 1990; 65:346–52
5. Jacobs JR, Reves JG: Effect site equilibration time is a determinant of induction dose requirement. Anesth Analg 1993; 76:1–6
6. Kazama T, Ikeda K, Morita K, Kikura M, Ikeda T, Kurita T, Sato S: Investigation of effective anesthesia induction doses using a wide range of infusion rates with undiluted and diluted propofol. ANESTHESIOLOGY 2000; 92:1017–28
7. Gentry WB, Krejcie TC, Henthorn TK, Shanks CA, Howard KA, Gupta DK, Avram MJ: Effect of infusion rate on thiopental dose–response relationships: Assessment of a pharmacokinetic–pharmacodynamic model. ANESTHESIOLOGY 1994; 81:316–24
8. Upton RN, Ludbrook GL, Grant C, Martinez AM: Cardiac output is a determinant of the initial concentrations of propofol after short-infusion administration. Anesth Analg 1999; 89:545–52
9. Kazama T, Ikeda K, Morita K, Ikeda T, Kikura M, Sato S: Relation between initial blood distribution volume and propofol induction dose requirement. ANESTHESIOLOGY 2001; 94:205–10
10. Ludbrook GL, Visco E, Lam AM: Propofol: relation between brain concentrations, electroencephalogram, middle cerebral artery blood flow velocity, and cerebral oxygen extraction during induction of anesthesia. ANESTHESIOLOGY 2002; 97:1363–70
11. Doufas AG, Bakhshandeh M, Bjorksten AR, Greif R, Sessler DI: Automated responsiveness test (ART) predicts loss of consciousness and adverse physiologic responses during propofol conscious sedation. ANESTHESIOLOGY 2001; 94:585–92
12. Doufas AG, Bakhshandeh M, Haugh GS, Bjorksten AR, Greif R, Sessler DI: Automated responsiveness test and bispectral index monitoring during propofol and propofol/N2O sedation. Acta Anaesthesiol Scand 2003; 47:951–7
13. Shafer SL, Gregg KM: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. J Pharmacokinet Biopharm 1992; 20:147–69
14. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88:1170–82
15. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. ANESTHESIOLOGY 1999; 90:1502–16
16. Doufas AG, Bakhshandeh M, Bjorksten AR, Greif R, Sessler DI: A new system to target the effect site during propofol sedation. Acta Anaesthesiol Scand 2003; 47:944–950
17. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51
18. Plummer GF: Improved method for the determination of propofol in blood by high- performance liquid chromatography with fluorescence detection. J Chromatogr 1987; 421:171–6
19. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. Clin Pharmacol Ther 1979; 25:358–71
20. Beal SL, Sheiner LB: NONMEM Users Guide, parts I and II. San Francisco, University of California, 1980
21. Varvel JR, Donoho DL, Shafer SL: Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm 1992; 20:63–94
22. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL: Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. ANESTHESIOLOGY 2003; 99:324–33
23. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G: Comparison of plasma compartment *versus* two methods for effect compartment–controlled target-controlled infusion for propofol. ANESTHESIOLOGY 2000; 92:399–406
24. Krejcie TC, Avram MJ: What determines anesthetic induction dose? It's the front-end kinetics, doctor! Anesth Analg 1999; 89:541–4
25. Chiou WL: Potential pitfalls in the conventional pharmacokinetic studies: effects of the initial mixing of drug in blood and the pulmonary first-pass elimination. J Pharmacokinet Biopharm 1979; 7:527–36
26. Avram MJ, Krejcie TC: Using front-end kinetics to optimize target-controlled drug infusions. ANESTHESIOLOGY 2003; 99:1078–86
27. Barvais L, Cantraine F, D'Hollander A, Coussaert E: Predictive accuracy of continuous alfentanil infusion in volunteers: Variability of different pharmacokinetic sets. Anesth Analg 1993; 77:801–10
28. Shafer SL, Varvel JR, Aziz N, Scott JC: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. ANESTHESIOLOGY 1990; 73:1091–102
29. Vuyk J, Engbers FH, Burm AG, Vletter AA, Bovill JG: Performance of computer-controlled infusion of propofol: An evaluation of five pharmacokinetic parameter sets. Anesth Analg 1995; 81:1275–82
30. Ludbrook GL, Upton RN, Grant C, Gray EC: Brain and blood concentrations of propofol after rapid intravenous injection in sheep, and their relationships to cerebral effects. Anaesth Intensive Care 1996; 24:445–52
31. Kuizenga K, Kalkman CJ, Hennis PJ: Quantitative electroencephalographic analysis of the biphasic concentration-effect relationship of propofol in surgical patients during extradural analgesia. Br J Anaesth 1998; 80:725–32
32. Kuizenga K, Proost JH, Wierda JM, Kalkman CJ: Predictability of processed electroencephalography effects on the basis of pharmacokinetic–pharmacodynamic modeling during repeated propofol infusions in patients with extradural analgesia. ANESTHESIOLOGY 2001; 95:607–15