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Comparison of Plasma Compartment versus Two Methods for Effect Compartment–controlled Target-controlled Infusion for Propofol

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***Background*:** Target-controlled infusion (TCI) systems can control the concentration in the plasma or at the site of drug effect. A TCI system that targets the effect site should be able to accurately predict the time course of drug effect. The authors tested this by comparing the performance of three control algorithms: plasma-control TCI *versus* two algorithms for effect-site control TCI.

Methods: One-hundred twenty healthy women patients received propofol *via* TCI for 12-min at a target concentration of 5.4 μg/ml. In all three groups, the plasma concentrations were computed using pharmacokinetics previously reported. In group I, the TCI device controlled the plasma concentration. In groups II and III, the TCI device controlled the effect-site concentration. In group II, the effect site was computed using a half-life for plasma effect-site equilibration ($t_{\frac{1}{2}} k_{e0}$) of 3.5 min. In group III, plasma effect-site equilibration rate constant (k_{e0}) was computed to yield a time to peak effect of 1.6 min after bolus injection, yielding a $t_{\frac{1}{2}} k_{e0}$ of 34 s. the time course of propofol was measured using the bispectral index. Blood pressure, ventilation, and time of loss of consciousness were measured.

Results: The time course of propofol drug effect, as measured by the bispectral index, was best predicted in group III. Targeting the effect-site concentration shortened the time to loss of consciousness compared with the targeting plasma concentration without causing hypotension. The incidence of apnea was less in group III than in group II.

Conclusion: Effect compartment–controlled TCI can be safely applied in clinical practice. A biophase model combining the Marsh kinetics and a time to peak effect of 1.6 min accurately predicted the time course of propofol drug effect.

(Key words: Adult population; anesthetics; female patient population; human population; intravenous propofol; modeling; time to peak effect; effect-site modeling; k_{e0}; population.)

TARGET-CONTROLLED infusion (TCI) devices for propofol incorporate an internal model of propofol pharmacokinetics to rapidly achieve and maintain a constant drug concentration in the plasma[1,2] or at the site of drug effect.[3,4] When a plasma concentration is targeted, an attempt is made to achieve a square wave in the plasma. The effect-site equilibrates with the half-life of ln2/plasma effect-site equilibration rate constant (k_{e0}). In turn, the target effect compartment concentration is approached slowly. In contrast, when the effect site is targeted, the plasma compartment must be overdosed initially to drive the drug into the effect site (fig. 1). The performance of TCI systems that target plasma drug concentration has been reported extensively.[5–16] Recently, Wakeling *et al.*[17] reported that targeting the effect-site concentration for propofol resulted in a more rapid loss of consciousness (LOC) without an increase in the risk of hypotension. The purpose of this study was to compare three different TCI control algorithms: plasma control (as currently implemented in the Diprifusor device developed by AstraZeneca, Manchester, England; effect-site control based on a k_{e0} of 0.20 min^{-1}, as reported by Billard *et al.*[18]; and effect-site control based on a time to peak effect of 1.6 min, as recently proposed by Schnider *et al.*[19] The time course of propofol drug effect was measured using the bispectral index (BIS).[20–23]

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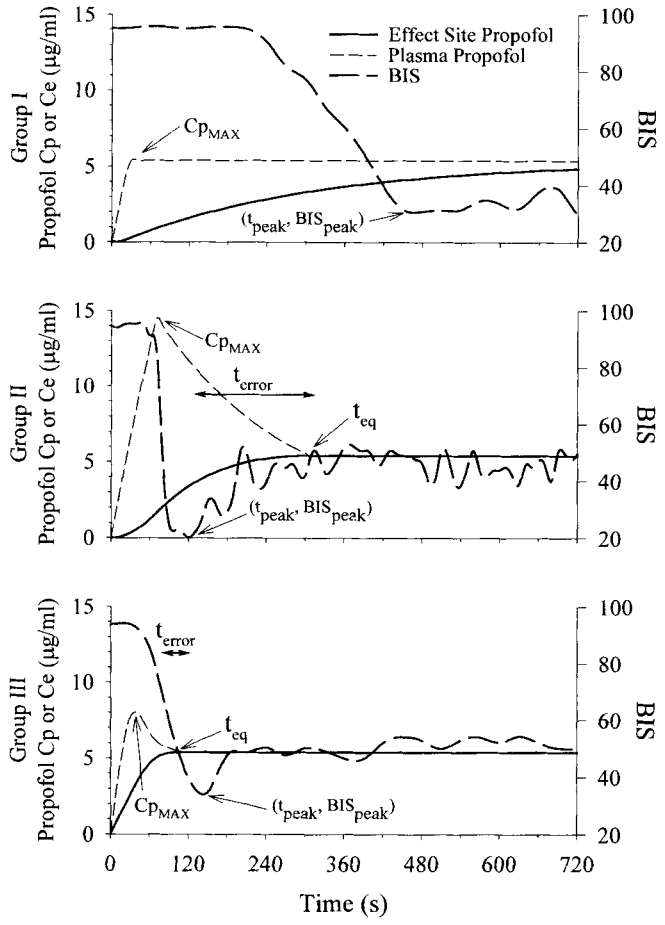

Fig. 1. Theoretical example of the applied parameters for evaluating the pharmacokinetics–pharmacodynamics model applied for each group. (*Upper*) Graph shows a group I example (plasma compartment controlled target-controlled infusion (TCI) at target concentration (C_T) = 5.4 μg/ml, Marsh model.[24] (*Middle*) Graph shows a group II example (effect compartment–controlled TCI at C_T = 5.4 μg/ml, biophase model using Marsh kinetics[24] and a k_{e0} of[18] 0.20 min^{-1}). (*Lower*) Shows a group III example (effect compartment–controlled TCI at C_T = 5.4 μg/ml, biophase model using Marsh kinetics[24] and a time to peak effect of 1.6 min).[19] Cp_{MAX} = maximum-reached calculated plasma concentration during infusion; t_{eq} = time (s) necessary for equilibration between predicted plasma propofol concentration calculated from the Marsh pharmacokinetics [Cp_{CALC}] and predicted effect-site propofol concentrations calculated from the Marsh pharmacokinetics and the estimates of k_{e0} [Ce_{CALC}]; t_{peak} = time (s) necessary for reaching maximal drug effect (lowest bispectral index [BIS]); t_{error} = t_{eq} − t_{peak}; BIS at t_{peak}.

Methods

Clinical Protocol

After Institutional Ethics Committee approval, informed consent was obtained from 120 women patients, American Society of Anesthesiologists physical status I and II, aged 18–60 yr, and scheduled for ambulatory gynecologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight; neurologic disorder; and use of psychoactive medication, including alcohol. Patients were allocated randomly to one of the three groups. In each group, the plasma pharmacokinetic model used was that reported by Marsh.[24] The Marsh model was chosen because of the good performance reported for this model by Coetzee *et al.*[25] More importantly, the Marsh pharmacokinetic model is incorporated into the Diprifusor propofol infusion device marketed in Europe, Australia, and Asia. The Diprifusor is the only commercially available TCI device and, therefore, evaluation of control algorithms based on the Marsh pharmacokinetic model represent potential commercial growth for the Diprifusor device.

Each patient received a 12-min infusion of propofol *via* the TCI device to a target level of 5.4 μg/ml. This was selected based on a report by Wakeling *et al.*[17] that a target amount of 5.4 μg/ml provided LOC in all volunteers and was able to distinguish plasma control from effect-site control. Previous studies by Smith[26] and Gepts[27] suggested that a propofol concentration of 5.4 μg/ml is associated with LOC in 95% of subjects.

In group I, the TCI device targeted the propofol concentration in the plasma, as presently implemented in the Diprifusor. An example of the anticipated propofol plasma and effect-site concentrations from this infusion method is shown in the top graph of figure 1 and is based on the pharmacokinetics reported by Marsh *et al.*,[24] and the propofol k_{e0} of 0.20 min^{-1} as reported by Billard *et al.*[18] In groups II and III, the TCI device targeted the propofol concentration at the site of drug effect using the strategy proposed by Shafer and Gregg[3] and the mathematical implementation reported by Jacobs and Williams.[4] In group II, the k_{e0} for plasma-effect site equilibration was 0.20 min^{-1}, as reported by Billard *et al.*[18] This value of k_{e0}, when combined with the propofol pharmacokinetics reported by Marsh, predicts a time to peak effect of 4.5 min after bolus injection. The middle graph of figure 1 shows an example of the expected plasma and effect-site concentrations for subjects in group II. For subjects in group III, we calculated the k_{e0} that predicted a time to peak effect 1.6 min after bolus injection, as reported by Schnider *et al.*[19] The calculation is an adaptation of the time-to-peak-effect algorithm reported by Shafer and Gregg[3] and implemented in the computer programs STANPUMP (written by S. Shafer, M.D., PAVMC, Palo Alto, CA) and RUGLOOP (written by T. De Smet, M.Sc., and M. Struys, M.D.,

Ph.D., Ghent University Hospital, Gent, Belgium)‡‡. In brief, k_{e0} is found using nonlinear regression to iteratively search out the value of k_{e0} that predicts the peak effect-site concentration at the desired time. The lower graph of figure 1 shows an example of the expected plasma and effect-site target concentrations for subjects in group III. Because subjects in group II were predicted to have much slower blood–brain equilibration than that of subjects in group III, the control algorithm called for larger doses in group II than in group III, resulting in the larger overshoot in plasma concentration seen in figure 1.

No premedication was given. Before anesthesia, an 18-gauge catheter was inserted in a large forearm vein for fluid and drug administration. The propofol infusion was connected as close as possible to the intravenous catheter to minimize dead space. Patients did not receive a loading dose of intravenous fluid before the propofol infusion and received 100–200 ml Ringer's lactate during the propofol infusion. No other drugs were administered during the 12 min of propofol administration. Patients received oxygen *via* face mask. The presence of apnea was recorded. If necessary, oxygen saturation as measured by pulse oximetry (Sp_{O_2} < 90%) manual breathing support using a circle system with 100% oxygen was applied. *Loss of consciousness* was defined as failure to respond to verbal command and was evaluated every 5 s.

Propofol concentrations were not measured. Rather, the analysis was based on the predicted plasma propofol concentration calculated from the Marsh pharmacokinetics (Cp_{CALC}) and on the predicted effect-site propofol concentrations calculated from the Marsh pharmacokinetics and the estimates of k_{e0} (Ce_{CALC}).[28] Three observations were made at the moment of LOC: time, BIS, and Ce_{CALC} (groups II and III only). We also calculated the propofol induction dose as the amount of propofol delivered to the patients up to the time of LOC.

Heart rate, end-tidal carbon dioxide, and Sp_{O_2} were measured every 10 s using the Datex AS3 (Datex, Helsinki, Finland). *Apnea* was defined as any interval in carbon dioxide exhalation exceeding 10 s. Blood pressure was measured every 30 s using the Datex monitor. Electroencephalographic BIS was measured every 10 s using an Aspect A-1000 EEG (Aspect Medical Systems, Natick, MA) monitor, version 3.2. Artifacts caused by poor signal quality were automatically detected and excluded from further analysis. All physiologic data were recorded by the RUGLOOP program (described below) and stored on hard disk.

Propofol was administered *via* a Graseby 3500 syringe pump (SIMS Graseby Ltd., Herts, England). The pump was controlled by RUGLOOP, a program written by the authors (T. D. S. and M. S.) in Visual C++ (Microsoft, Redmond, WA) for Windows 95/NT operating system (Microsoft). This TCI program can also be used as data management system. RUGLOOP incorporates algorithms to target the plasma[2] and the site of drug effect.[3] The algorithms in RUGLOOP, including those to target the effect site using k_{e0} (group II) and time to peak effect (group III) are adapted from STANPUMP.

Evaluation of the Pharmacokinetics–Pharmacodynamics Model

For all patients, the calculated plasma concentration, calculated effect-site concentration, infusion rate, and cumulative dose of propofol were recorded every 10 s and stored on hard disk. The performance of the systems was evaluated using the following measures, as illustrated in figure 1:

- t_{peak} = observed time necessary for reaching maximal drug effect (lowest BIS), taken within 2 min of LOC. Patients receiving propofol targeting the effect site (groups II and III) should have a faster onset of drug effect than patients receiving propofol targeting the plasma (group I). Therefore, this was our primary outcome measure for comparison of group I with groups II and III.
- t_{eq} = calculated time necessary for equilibration between Cp_{CALC} (the plasma propofol concentration) and Ce_{CALC} (the effect-site propofol concentration). This was not calculated for group I, in which Ce_{CALC} should only approach Cp_{CALC} asymptotically and, thus, t_{eq} is infinite.
- $t_{error} = t_{eq} - t_{peak}$. Using a value of k_{e0} calculated to give the correct time to peak effect should more accurately reflect the observed time course of drug effect than using a k_{e0} taken from the literature. If the effect-site model is accurate, the calculated time to equilibration should be similar to the observed time of peak effect. Therefore, t_{error} was our primary outcome measurement for comparison of group II with group III.
- Cp_{MAX} = calculated maximum plasma propofol concentration.
- BIS_{peak} = observed BIS at t_{peak}.

‡‡ STANPUMP and RUGLOOP are available at http://pkpd.icon.paloalto.med.va.gov

Table 1. Demographic Data

	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)
Age (yr)	37 ± 11	39 ± 12	35 ± 8
Weight (kg)	62 ± 10	62 ± 10	61 ± 8
Height (cm)	164 ± 7	166 ± 6	166 ± 6

Mean ± SD

- t_{MinMAP} = observed time to lowest arterial blood pressure (the "onset of side effect").

Statistical Analyses

Data were presented as the mean ± SD or as the median (range). Differences between the groups for the primary outcome measure were determined using a Wilcoxon rank sum test, as was the comparison in time to lowest blood pressure between groups II and III. Differences for secondary measures were assessed using Student two-tailed *t* tests after confirming that the data were normally distributed, except for the change in blood pressure, which was analyzed using analyses of variance for repeated measures. Significance level was set at 5%. The incidence of apnea was analyzed using the chi-square test.

Graphical Analysis

For visual comparison of the time course of drug effect, we graphed the propofol plasma concentration, BIS, and mean arterial pressures over time for all subjects. For subjects in groups II and III, we also graphed the effect-site concentrations over time.

Results

Population demographics for the three groups are shown in table 1. There were no significant differences among the three groups. No patients were excluded from the analysis. All data captured by the recording system were included in the analysis.

The observations made at the time of LOC are shown in table 2. As expected, patients lost consciousness more slowly when the TCI device targeted the plasma (90 s; range, 44–601 s) than when the device targeted the effect site (68 s [range, 45–104 s] and 71 s [range, 43–110 s] for groups II and III, respectively). The largest doses of propofol were administered in patients in group II. Patients in group III received a similar induction dose as the plasma-controlled TCI patients (group I). Patients in groups II and III lost consciousness at similar values of

Table 2. Observations at Loss of Consciousness (mean ± SD)

	Group I	Group II	Group III
Time (s)	90 (44–601)	68 (45–101)†	71 (43–110)†
BIS	67 ± 12	78 ± 11†	77 ± 11†
Ce_{CALC} (μg/ml)	Not calculated	1.8 ± 0.7‡	4.7 ± 0.6‡
Propofol induction dose (ml)	11.4 ± 3.9*	20.4 ± 3.6*	11.7 ± 2.0*

The propofol dose is the amount of drug given by the TCI device up to the moment of loss of consciousness.

* = $P < 0.05$ between I and II and between II and III.

† = $P < 0.05$ compared with group I.

‡ = $P < 0.05$ between groups II and III.

BIS = bispectral index; Ce_{CALC} = calculated effect-site concentration.

Table 3. Measures of Algorithm Performance

	Group I	Group II	Group III
t_{peak} (s)	218 ± 86	116 ± 21‡§	120 ± 21‡§
t_{eq} (s)	Not calculated	330 ± 36	130 ± 17
t_{error} (s)	Not calculated	207 ± 73‖	9 ± 15‖
Cp_{MAX} (μg/ml)	5.4 ± 0*	14.2 ± 0.4*	7.5 ± 0.2*
BIS at t_{peak}	39 ± 11†	27 ± 11†	41 ± 16†
t_{MinMAP} (s)	201 ± 70	165 ± 66§	329 ± 140§

* = $P < 0.05$ among all groups.

† = $P < 0.05$ between I and II and between II and III.

‡ = $P < 0.05$ compared with group I.

§ = $P < 0.05$ between t_{peak} and t_{MinMAP}.

‖ = $P < 0.05$ between II and III.

t_{peak} = observed time necessary for reaching maximal drug effect (lowest BIS), taken within 2 min of the loss of consciousness ; t_{eq} = calculated time necessary for equilibration between Cp_{CALC} (the plasma propofol concentration) and Ce_{CALC} (the effect-site propofol concentration). This was not calculated for group I, in which Ce_{CALC} should only approach Cp_{CALC} asymptotically, and therefore t_{eq} is infinite ; $t_{error} = t_{eq} - t_{peak}$; Cp_{MAX} = calculated maximum plasma propofol concentration ; BIS_{peak} = observed BIS at t_{peak} ; t_{MinMAP} = observed time to lowest arterial blood pressure (the "onset of side-effect").

BIS. However, the calculated effect-site concentration in group II was only 1.8 ± 0.7 μg/ml, significantly less than the calculated effect-site concentration of 4.7 ± 0.6 in group III.

The measures to evaluate the performance of the three infusion algorithms can be found in table 3. Onset was significantly faster when the effect site was targeted (116 ± 21 and 120 ± 21 s in groups II and III, respectively) than when the plasma concentration was targeted (218 ± 86 s). The error in predicting the time of peak effect was 207 ± 73 s in group II and 9 ± 15 s in group III, a difference that was highly significant ($P < 0.0001$). Group II was associated with the largest overshoot in

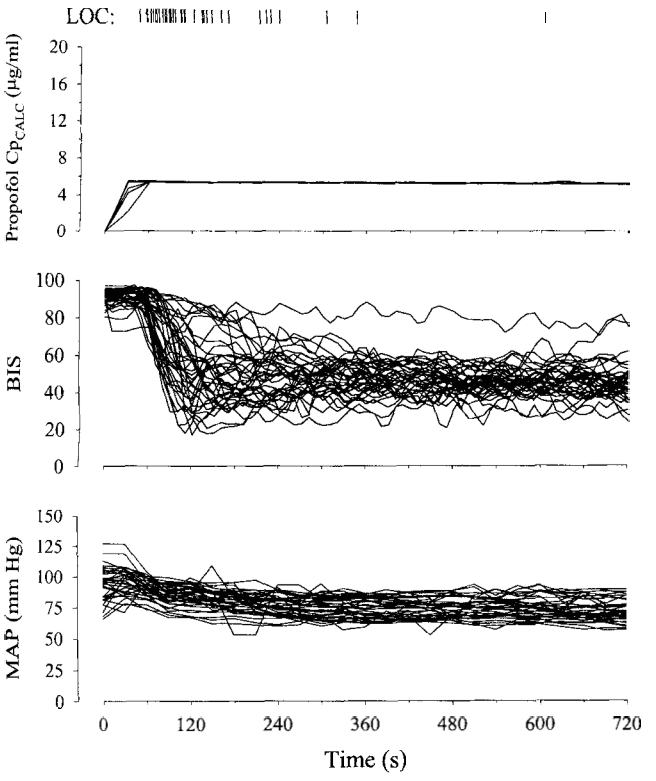

Fig. 2. Individual data from group I (plasma compartment-controlled target-controlled infusion [TCI] at C_T = 5.4 μg/ml, Marsh model).[24] Visual comparison of the time course of drug effect. Graphed is the moment of loss of consciousness (LOC), the propofol plasma concentration, bispectral index, and mean arterial pressures over time for all subjects. (Individual curve variability for predicted plasma propofol concentration calculated from the Marsh pharmacokinetics [Cp_{CALC}] is found to be caused by variability in anthropometric data, limited maximum infusion rate of the syringe pump, and time interval of 10 s for data acquisition.)

plasma propofol concentration (14.2 ± 0.4 μg/ml) and the lowest BIS (27 ± 11), both significantly different from groups I and III. The peak cardiovascular depression shown in table 3 occurred significantly later than the peak electroencephalography (EEG) depression in groups II and III ($P < 0.05$).

Figures 2, 3, and 4 show the time course of propofol concentration, BIS, and mean arterial pressure in all patients. The vertical bars on the top show the times of LOC. There was considerably more variability in group I than in groups II or III in the time to LOC. Group II was characterized by a larger plasma overshoot and a more precipitous decrease in BIS and blood pressure than was observed in groups I or III. In group III, the decrease in BIS was as rapid as in group II, but not as large. With the exception of the more rapid change in blood pressure observed in group II, the blood pressure response was similar in all three groups. There were no significant changes in heart rate from baseline in any of the groups.

Significantly more patients experienced apnea in group II (34 or 40 patients) than in groups I (9 of 40 patients) or III (17 of 40 patients). Eight patients in group II required manual ventilation. In the other groups, spontaneous ventilation resumed before manual ventilation was necessary.

Discussion

The purpose of this study was to compare three methods of propofol administration *via* TCI. The first method

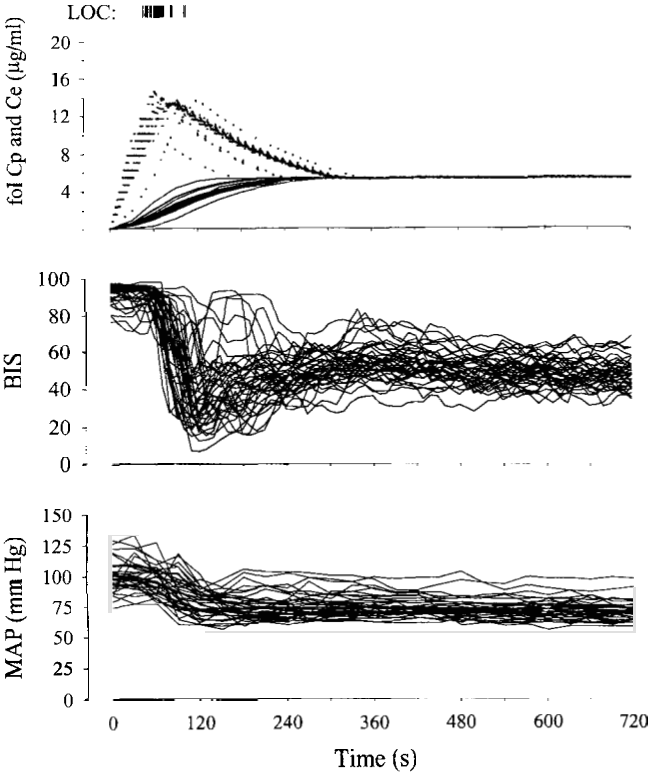

Fig. 3. Individual data from group II (effect compartment–controlled target-controlled infusion [TCI] at C_T = 5.4 μg/ml, biophase model using Marsh kinetics[24] and a k_{e0} of[18] 0.20 min^{-1}). Visual comparison of the time course of drug effect. Graphed is the moment of loss of consciousness (LOC), the propofol plasma (dashed line) and effect-site concentration (solid line), bispectral index, and mean arterial pressures over time for all subjects. (Individual curve variability for predicted plasma propofol concentration calculated from the Marsh pharmacokinetics [Cp_{CALC}] is found to be caused by variability in anthropometric data, limited maximum infusion rate of the syringe pump, and time interval of 10 s for data acquisition.)

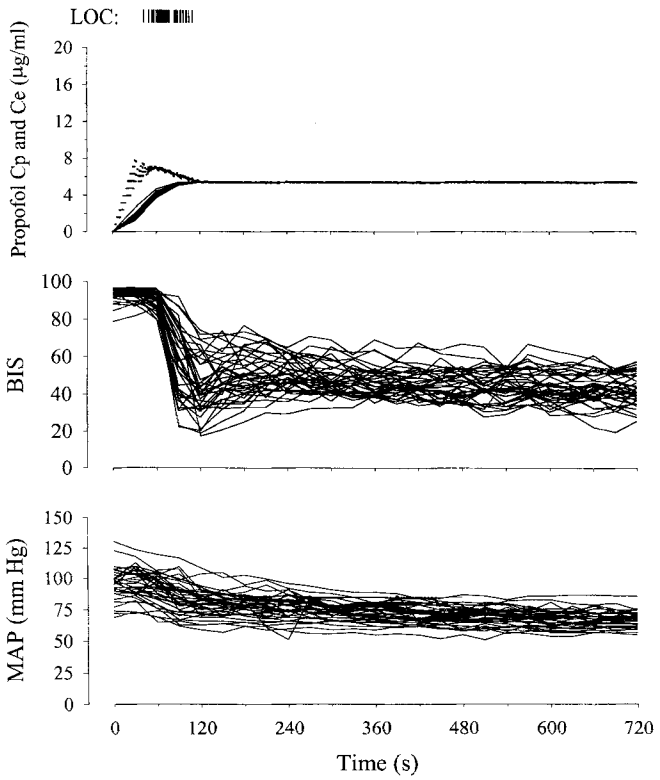

Fig. 4. Individual data from group III (effect compartment–controlled target-controlled infusion [TCI] at C_T = 5.4 μg/ml, biophase model using Marsh kinetics[24] and a time to peak effect of 1.6 min.)[19] Visual comparison of the time course of drug effect. Graphed is the moment of loss of consciousness (LOC), the propofol plasma (dashed line) and effect-site concentration (solid line), bispectral index, and mean arterial pressures over time for all subjects. (Individual curve variability for predicted plasma propofol concentration calculated from the Marsh pharmacokinetics [Cp_{CALC}] is found to be caused by variability in anthropometric data, limited maximum infusion rate of the syringe pump, and time interval of 10 s for data acquisition.)

reproduced the performance of the commercially available Diprifusor device, which was designed to control the plasma propofol concentration. The second two methods evaluated the performance of a device that targeted the concentration in the effect site rather than in the plasma. Our results confirmed the findings published by Wakeling *et al.*[17] When a TCI device targets the effect site, onset of drug effect is hastened without adverse hemodynamic consequences. The peak cardiovascular depression occurred significantly later than did the peak EEG depression in groups II and III. As a result, targeting the effect site does not increase toxicity because the toxicity has a slower equilibration than does the desired effect. Our results confirm prospectively those by Kazama *et al.*,[29] who found that the effect of propofol on BIS occurs more rapidly than its effect on systolic blood pressure. In addition, there was less variability and, hence, potentially greater predictability in the time to LOC when the effect site was targeted.

There are several ways that the equilibration delay between the plasma and the site of drug effect can be added to the pharmacokinetic model. The most straightforward approach is to introduce an effect-site model using the value of k_{e0} from a previously published report. This is the approach taken in group II. As pointed out by Gentry *et al.*,[30] the value of k_{e0} is highly influenced by the pharmacokinetic model; therefore, it may be unwise to mix the k_{e0} from one study with the pharmacokinetics from a different study. It is possible to directly observe the time to peak effect; therefore, this is a "model-independent" descriptor of blood-brain equilibration. The time to peak effect is experimentally verifiable by giving a bolus and using an appropriately sensitive measure of drug effect.[19] Time to peak effect can be used to establish the appropriate value of k_{e0} for use with any pharmacokinetic model or, indeed, any representation of the bolus response (*e.g.*, a set of time *vs.* concentration data points), provided that a submaximal effect is elicited and that the time of peak effect can be observed precisely. Schnider *et al.*[19] reported a time to peak propofol effect of 1.6 min, based on close inspection of the EEG waveform in 48 subjects. We calculated that a k_{e0} of 1.21 min^{-1} would produce a peak effect-site concentration of 1.6 min when using the Marsh pharmacokinetics. The resulting value of k_{e0} was prospectively tested in group III. Group III performed better than did group II in this study. The algorithm in group III more accurately predicted the time of peak EEG effect. It also provided an anesthetic induction with less drug, less of an overshoot with BIS, less apnea, and a more gradual decrease in blood pressure than in group II. These results show that the clinical outcome is dependent on the value of k_{e0}. This also validates the use of the time-to-peak-effect concept as a pharmacodynamic parameter.

Because the BIS is a continuous measure of propofol drug effect, we chose to use it as the primary measure of the time course of drug effect rather than a more clinically oriented measure, such as the time of LOC. Doi *et al.*[20] demonstrated a correlation (r^2 = 0.55) between BIS and calculated blood concentrations of propofol, and others confirmed these results.[21–23] The BIS is calculated using a 30-s rolling window and, thus, lags behind the current status of the patient by approximately 15 s. This

may account for the observation in table 2 of lower BIS values for LOC for subjects in group I than those in group II and group III, and for the somewhat longer time to peak BIS effect in group III than the predicted time to peak effect.

The equilibration delay between the plasma and the site of drug effect is a physiologic reality. Incorporating this delay into a TCI device increases the complexity of the pharmacokinetic model used to control the infusion. However, if the delay is ignored, the model relating dose to drug effect is fundamentally incorrect. A TCI device programmed with an incorrect model cannot be expected to produce the desired time course of drug effect.

In conclusion, we demonstrated that a TCI device that controlled the concentration at the site of drug effect more accurately produced the desired time course of drug effect than did a device that only controlled plasma drug concentration. We also demonstrated that the choice of plasma effect-site equilibration delay makes a difference in the performance of the device. It is not appropriate to use a documented value of k_{e0} in an infusion device without consideration of the corresponding pharmacokinetic model. Future studies will be needed to determine the combined pharmacokinetic-pharmacodynamic model that best predicts the time course of propofol drug effect.

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