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Targeting Effect Compartment or Central Compartment Concentration of Propofol

What Predicts Loss of Consciousness?

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Background: **An effect compartment has been postulated, and the k_{e0} has been quantified for several intravenous anesthetic drugs using electroencephalography (EEG) as the measure of effect. The authors wanted to validate that loss of responsiveness (LOR) was related to targeting an effect compartment concentration rather than a central compartment (plasma) concentration.**

Methods: **Twenty American Society of Anesthesiologists physical status I and II patients were randomized to receive propofol administered to a target central compartment or target effect compartment site concentration of 5.4 μg/ml propofol administered by a target-controlled infusion (TCI) using a previously validated set of pharmacokinetic parameters and a k_{e0} of 0.63 min^{-1}. Every 30 s for the first 5 min and every minute for the second 5 min the patients were asked to open their eyes. The time to LOR was measured by a blinded investigator. The authors also simulated the time to reach the desired target effect site concentration using varying k_{e0} values.**

Results: **The median time to LOR in the group targeted to a predicted plasma propofol concentration was 3.02 min and 1.23 min in the group targeted to a predicted effect compartment propofol concentration ($P < 0.05$). LOR to command in both groups occurred at a predicted median effect compartment concentration of 4.55 μg/ml. Simulations demonstrated that the time predicted to LOR targeting an effect site concentration of 5.4 μg/ml is markedly altered by the value chosen for the k_{e0}.**

Conclusions: **This study confirms the utility of the k_{e0} value to describe the effect compartment for propofol. The authors also illustrate the importance of selecting the correct k_{e0} value for the pharmacokinetic parameters used within the TCI system. (Key words: Anesthetics; computers; intravenous; pharmacokinetics.)**

THE development of a computerized pharmacokinetic model-driven infusion device was first described by Helmut Schwilden in 1981.[1] He showed that it was possible to attain the desired plasma concentration of an intravenous anesthetic drug by using a computer-controlled pump programmed with the published pharmacokinetics of the drug. The plasma concentration of intravenous anesthetic drugs after a bolus peaks virtually instantaneously; however, the peak effect of the drug occurs later when the brain concentration equilibrates with the central compartment (plasma). This delay or hysteresis is because the site of action is at the biophase, the immediate milieu where the drug acts (receptors, enzymes, and membranes), rather than at the plasma.

The biophase or effect site has its own pharmacokinetic parameters within the traditional three-compartment model. The rate constant k_{e0} describes the removal of the drug from the effect site. If a constant plasma concentration (in this manuscript *plasma concentration* refers to calculated central compartment concentration) is maintained, then the time for the effect site concentration to reach 50% of the plasma concentration is given by $0.693/k_{e0}$. Thus, the k_{e0} can be incorporated into the traditional three-compartment model to calculate the dosing scheme to achieve a desired effect site rather than a target plasma concentration.[2–4] The k_{e0} has been estimated from the electroencephalographic (EEG) response to propofol. The validity of using an EEG-derived k_{e0} to provide a desired effect has not been tested prospectively. We therefore wanted to determine if targeting an effect site, rather than a central compartment concentration, would better predict loss of responsiveness.

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Table 1. Pharmacokinetic Values Used in CaCl for the Administration of Propofol

Parameter	Value
V1 (L/kg)	0.0767
k10 (min)	0.3035
k12 (min)	0.2846
k21 (min)	0.0866
k13 (min)	0.2730
k31 (min)	0.0036
K_{e0} (min^{-1})	0.63

Methods

The study was approved by the institutional review board of Duke University Medical Center. Twenty patients of either gender, American Society of Anesthesiologists physical status I or II, and aged 18–55 yr signed a written, informed consent and were entered into the study. Exclusion criteria included weight greater than 150% of ideal, history of esophageal reflux, and patients on any form of chronic pain or central nervous system medication. Patients were not premedicated before induction of anesthesia.

Patients were randomized to have propofol administered *via* computer-assisted continuous infusion (CACI)[5] to either a target plasma propofol concentration (group P) or to target effect site (group E) propofol concentration. In both groups the TCI system displays both the targeted effect and central compartment concentration. These were used later to determine the calculated effect site concentration at each time interval when a central compartment concentration was targeted and *vice versa.* The propofol was administered by TCI using the pharmacokinetic parameters shown in table 1.[6] The accuracy of these pharmacokinetic parameters have previously been validated showing a bias of 2% and an median absolute performance error of 30%.[7] The maximum infusion rate of the pump of the TCI system is 1000 ml/h. In neither group was an actual blood sample taken to measure plasma propofol concentrations.

Although the time for equilibration between the central compartment and the effect compartment is fixed, the k_{e0} determined from pharmacokinetic and pharmacodynamic studies is a function of the pharmacokinetic parameters derived at the same time. Although a k_{e0} for propofol had been published, its value when combined with the pharmacokinetic parameters of propofol that were being used within our TCI system had not. An estimated value for k_{e0} was determined. The value used for k_{e0} was 0.63 min^{-1}.

The concentration targeted for all subjects was 5.4 μg/ml. This central compartment concentration when equilibrated with its effect site has been shown to represent the CP_{95} for loss of consciousness.[7,8] The following monitors were applied: electrocardiograph, pulse oximeter, noninvasive blood pressure, and capnograph. An intravenous catheter was inserted for intravenous fluid and propofol administration. After preoxygenation, 40 mg of intravenous lidocaine was given, and the TCI pump was started. The blood pressure and heart rate were recorded every 30 s for the first 5 min and then each minute for the final 5 min.

The time to loss of responsiveness (LOR) was assessed by a blinded investigator asking the patients in a loud voice to open their eyes every 30 s and documenting the time that they failed to do so. The patients' ventilation was assisted as appropriate to maintain the end-tidal CO_2 partial pressure between 35 and 40 mmHg. The study was terminated 10 min from the start of the infusion.

The mean and median time to LOR was calculated. These were compared using unpaired *t* test. Hemodynamic values were compared using analysis of variance (ANOVA) and repeated measures ANOVA. Logistic regression of time to LOR data was carried out by first tabulating binary response data for each patient. The data took the form of "no response" at 30-s intervals up to the point when LOR occurred. The time of LOR was labeled a "response." The resulting binary data were compiled in an Excel spreadsheet (version 7.0, Microsoft Corp, Redmond, WA). A standard logistic regression equation was fit to the data using the solver function to manipulate the values of the steepness factor and C_{50} while maximizing log likelihood. The procedure was conducted separately for each target group (plasma and effect).

Using the logistic curves described previously, the times to achieve a given probability of LOR were tabulated for each target group. Probabilities of 0.1–0.9 were examined at 0.1-intervals plus an additional data point at 0.95 (10 data points total). Times associated with these probabilities were then matched to the effect site concentration predicted by CACI for each time point. The percentage differences between the two predicted effect site concentrations at each time point were tabulated according to:

$$\% \text{ difference} = \frac{| C_{eff}t - C_{eff(plasma)}t | \cdot 100}{| C_{eff\,(effect)}t |}$$

where C_{eff} is the predicted effect site concentration for the effect site targeted group and $C_{eff(plasma)}$ is the same

Table 2. Loss of Responsiveness (LOR): Demographic and Hemodynamic Variables in the Target Central Compartment and Target Effect Compartment Groups

	Target Plasma	Target Effect
Age (yr) (mean ± SD)	32.7 (8.9)	28.6 (7.8)
Gender (M/F)	7/3	6/4
Weight (kg) (mean ± SD)	76.5 (15.3)	72.3 (9.7)
Med LOR time (min)	3.02	1.23*
Estimated effect site concentration at LOR (μg/ml)	4.5	4.7
Maximum % change in MAP (mean)	−28	−23
Maximum % increase in heart rate (mean)	+18	+17
Maximum % reduction in heart rate (mean)	−6	−13
Dose of propofol to LOR (mg) (mean ± SD)	142.9 (40.1)	141.2 (39.8)

* $P < 0.05$ per unpaired t test.

for the group targeted to a central compartment/plasma concentration.

Simulations of predicted effect site concentrations were performed for different values of k_{e0}. This was accomplished by importing the CACI infusion rates for both plasma target and effect target groups into an Excel spreadsheet. PKPD Tools for Excel[9]‖ were then programmed to predict effect site concentration using the identical pharmacokinetic parameters from the original CACI infusions. Additional simulations were then performed by altering the k_{e0} value from 0.63 min^{-1} (original value) to 0.5, 0.4, 0.3, and 0.2. All other kinetic parameters were not altered.

Results

The demographics were similar between the two groups (table 2). The mean age in group P was (mean ± SD) 32.7 ± 8.9 yr, and 28.6 ± 7.8 yr in group E (P = NS). The mean weight in group P was 76.5 ± 15.3 kg and 72.3 ± 9.7 kg in group E (P = NS).

The median time to LOR in group P was 3.02 min and 1.23 min in group E ($P < 0.05$; fig. 1). The predicted effect site concentration of propofol at the time of LOR was 4.5 μg/ml in group P and 4.7 μg/ml in group E (P = NS). The mean (± SD) total dose of propofol administered until LOR was 142.9 ± 40.1 mg in group P and 141.2 ± 39.8 mg in group E ($P \geq 0.05$). The 50% probability of LOR occurred at 76 s for the effect targeted group, at which time the predicted effect site concentration was 4.58 μg/ml. For the plasma targeted group, the corresponding values were 172 s and 4.42 μg/ml. The predicted effect site concentration *versus* probability of LOR derived from the patients in each group is plotted in figure 2. The difference in effect site concentration between the two groups at any probability of LOR did not exceed 15%. The simulated times to

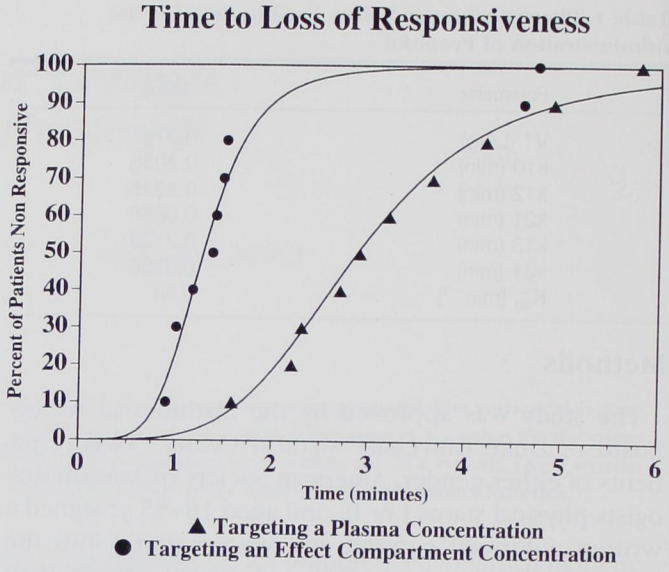

Fig. 1. The time to loss of response to a verbal stimulus when patients were administered propofol to a target plasma or target effect site concentration of 5.4 μg/ml.

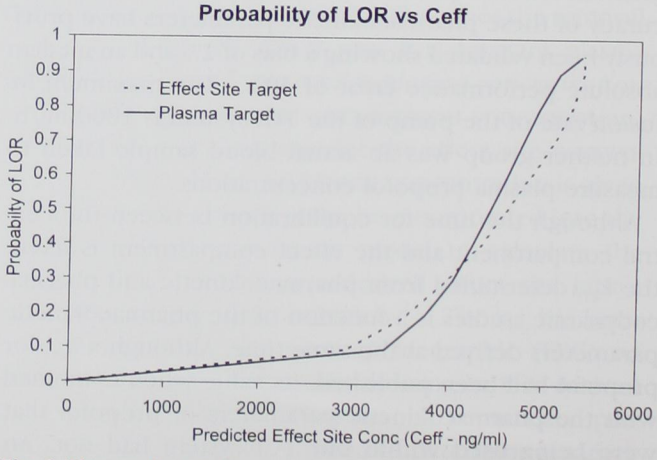

Fig. 2. The predicted effect site concentration *versus* probability of loss of response at the time patients no longer responded to a verbal stimulus when administered propofol to either an effect or plasma concentration of 5.4 μg/ml.

‖ An Excel 5.0 program written by Charles Minto and Thomas Schnider; available at anonymous FTP from pkpd.icon.palo-alto.med.va.gov or by the WWW at URL:http://pkpd.icon.palo-alto.med.va.gov.

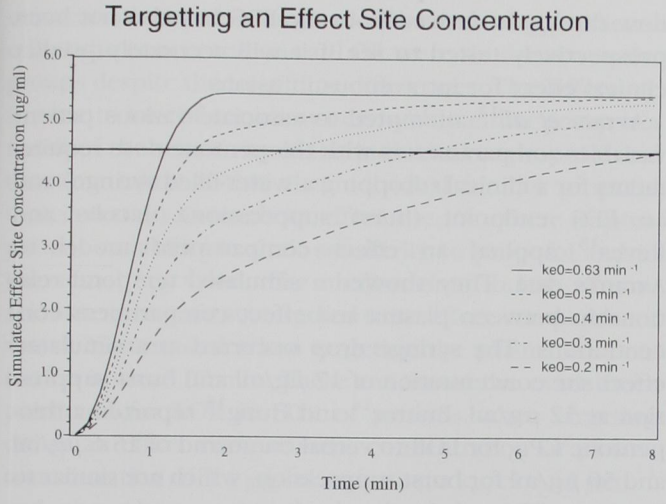

Fig. 3. Simulated times to achieve effect compartment concentrations when using differing k_{e0} values with the pharmacokinetics of Gepts and Camu[6] and targeting an effect compartment concentration of 5.4 μg/ml propofol.

achieve effect compartment concentrations when using differing k_{e0} values with the pharmacokinetics of Gepts and Camu[6] and targeting an effect compartment concentration of 5.4 μg/ml propofol is presented in figure 3. The time to achieve the Cp_{50} of 4.5 μg/ml increases from 1.3 min for a k_{e0} of 0.63 min^{-1} to 7.5 min for a k_{e0} of 0.2 min^{-1}. Figure 4 illustrates the simulated times to achieve effect compartment concentrations when using differing k_{e0} values with the pharmacokinetics of Gepts and Camu[6] and targeting a central compartment concentration of 5.4 μg/ml propofol. At a k_{e0} of 0.63 min^{-1} the

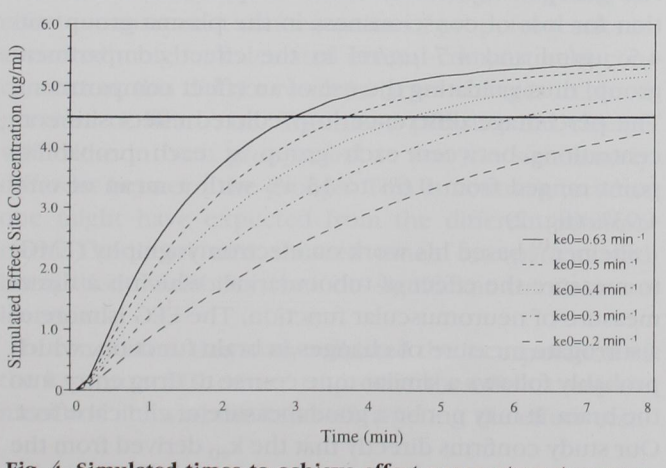

Fig. 4. Simulated times to achieve effect compartment concentrations when using differing k_{e0} values with the pharmacokinetics of Gepts and Camu[6] and targeting a central compartment concentration of 5.4 μg/ml propofol.

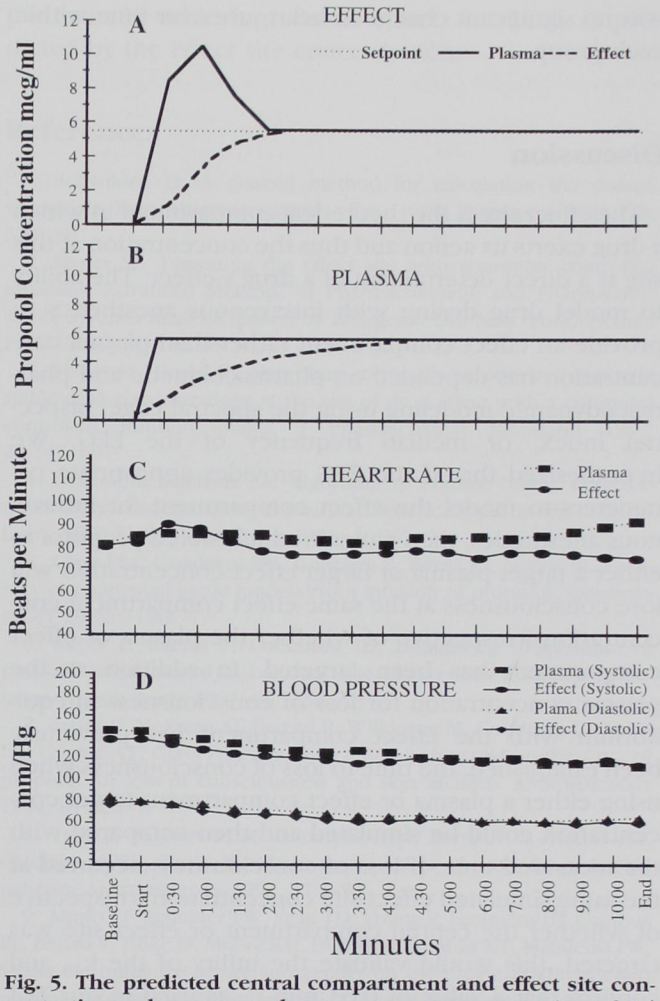

Fig. 5. The predicted central compartment and effect site concentrations when a central compartment concentration of 5.4 μg/ml is targeted (*panel A*) and the predicted central compartment and effect site concentrations when an effect compartment concentration of 5.4 μg/ml is targeted (*panel B*). The resultant changes in blood pressure (*panel C*) and heart rate (*panel D*) over time for both groups.

time to achieve the effect site Cp_{50} of 4.5 μg/ml is 3 min and increases to more than 8 min when the k_{e0} is 0.2 min^{-1}.

The hemodynamic and simulated plasma effect site concentrations of a typical patient in the plasma and effect site groups and the average changes in blood pressure (systolic/diastolic) and heart rate are plotted in figure 5. There were no significant differences in the hemodynamic variables between the 2 groups during the 10 min of the study. In both groups blood pressure decreased over time ($P < 0.05$). The maximal decrease in each individual's mean arterial blood pressure averaged 25% in group P and 23% in group E (P = NS). There

was no significant change in heart rate over time within each group.

Discussion

The effect site is the theoretical compartment in which a drug exerts its action and thus the concentration at this site is a direct determinant of a drug's effect. The ability to model drug dosing with intravenous anesthetics to provide an effect compartment rather than plasma concentration has depended on pharmacokinetic and pharmacodynamic modeling using the spectral edge, bispectral index, or median frequency of the EEG. We hypothesized that if the EEG provides appropriate parameters to model the effect compartment for intravenous anesthetics, then patients administered propofol to either a target plasma or target effect concentration will lose consciousness at the same effect compartment concentration irrespective of whether the plasma or effect compartment has been targeted. In addition as the plasma concentration for loss of consciousness in equilibrium with the effect compartment has previously been established, the time to loss of consciousness when using either a plasma or effect compartment target concentration could be simulated and then compared with the measured time. If loss of consciousness occurred at the same simulated effect site concentration irrespective of whether the central compartment or effect site was targeted, this would validate the utility of the k_{e0} and confirm that a value of 0.63 min^{-1}, as used in our TCI device, is appropriate when combined with the pharmacokinetic parameters of Gepts and Camu.[6]

The effect compartment model was developed by Sheiner *et al.*[10] in 1979 to account for the hysteresis between the time course of plasma concentration and the time course of drug effect. Sheiner *et al.*[10] tested the model using infusions of tubocurarine in healthy volunteers and renal failure patients. They demonstrated that they could accurately characterize the relationships between tubocurarine plasma concentration and effect. The k_{e0} was shown to characterize the temporal aspects of drug equilibrium with the site of action. This also enabled estimation of the half-time of equilibration of the plasma concentration and drug effect by calculating the T1/2 k_{e0}.They however did not prospectively test the validity of the k_{e0} that they had derived.

Stanski[11] using similar methodology subsequently used the EEG to determine the k_{e0} for intravenous anesthetics such as thiopentone, opiates, and benzodiazepines. Until now the k_{e0} as derived from the EEG has also not been prospectively tested to see if it will accurately predict clinical effect for intravenous infusions.

Avram *et al.*[12] attempted to associate various patient variables and parameters with thiopentone dose requirements for a clinical (dropping a water-filled syringe) and an EEG endpoint (burst suppression). Jacobs and Reves[13] applied an effect compartment model to Avram's data. They showed a simulated temporal relationship between plasma and effect compartment concentrations. The syringe drop occurred at a simulated effect site concentration of 17 μg/ml and burst suppression at 52 μg/ml. Buhrer[14] and Hung[15] reported a thiopentone CP_{50} for LOR to verbal command of 15.6 μg/ml and 50 μg/ml for burst suppression, which are similar to Jacobs and Reves' simulated values.

Our study is somewhat different because it provides formal proof through a prospective design of the utility of the k_{e0} in predicting clinical effect whether the effect site or the plasma concentration is targeted. We administered propofol *via* a target-controlled infusion device. The targeted concentration for all patients was 5.4 μg/ml, a previously derived Cp_{95} concentration.[6] Half the patients were targeted to a plasma concentration and the other half to an effect site concentration of propofol. All patients had lost consciousness when their simulated effect compartment concentration reached 5.4 μg/ml. The probability of LOR when compared with the predicted effect site propofol concentration was similar in both groups (*i.e.*, once the effect compartment concentration was considered the variability in the concentration for loss of consciousness was identical between the two groups. The median effect compartment concentration for loss of consciousness in the plasma group was 4.5 μg/ml and 4.7 μg/ml in the effect compartment group, thus validating the use of an effect compartment. The percentage difference in predicted effect site concentrations between each group at each probability point ranged from 0.6% to 13.4% with a mean of only 4.93% (fig. 2).

Sheiner[10] based his work on electromyography (EMG) to measure the effect of tubocurarine, which is a direct measure of neuromuscular function. The EEG is more of a surrogate measure of changes in brain function, which probably follows a similar time course to drug entry into the brain. It may not be a good measure of clinical effect. Our study confirms directly that the k_{e0} derived from the EEG for propofol does predict the clinical effect of LOR or loss of consciousness. The median times to LOR were significantly different when the plasma or effect site

concentrations were targeted. However, the predicted effect site concentrations at LOR were similar across the groups despite the large time differences. The difference in time to loss of consciousness within either group is a result of the sensitivity of the individual to propofol and the time taken within the individual for the propofol concentration to reach its effect site, *i.e.*, there is interpatient variability in their sensitivity to propofol and in the actual k_{e0} value. The median time to loss of consciousness in patients targeted to an effect compartment was 1.23 min, and when targeting the plasma concentration it was 3.02 min. These are almost the exact times predicted for LOR in 50% of patients when targeting either an effect compartment concentration or plasma concentration of 5.4 μg/ml and using a k_{e0} of 0.63 min^{-1} and the pharmacokinetic parameters of Gepts and Camu. As the k_{e0} value of 0.63 min^{-1} accurately predicted the time of LOR this study prospectively validated this value when combined with the pharmacokinetic parameters that were used. Reducing the k_{e0} to below 0.63 min^{-1} would predict much slower times to loss of consciousness (figs. 3 and 4). Through these simulations we have also indirectly confirmed that the k_{e0} depends on the pharmacokinetic parameters with which it is being used. Thus although a k_{e0} of 0.63 min^{-1} is correct when using the pharmacokinetic parameters of Gepts and Camu, it will not necessarily be the correct k_{e0} value when using any other pharmacokinetic parameters. It will be important, as an effect compartment is incorporated into TCI devices, that the k_{e0} value used with other pharmacokinetic parameters is prospectively tested to confirm its accuracy.

We also demonstrated that even though targeting an effect compartment concentration of propofol results in a markedly higher calculated central compartment concentration, this did not result in larger changes in blood pressure or heart rate. The blood pressure did change with time in both groups, but it was not significantly different between the groups. This is contrary to what one might have expected from the different infusion rates. The heart rate showed much interpatient and intrapatient variability, but no significant trends were identified.

In conclusion, this study validated the incorporation of the k_{e0} into a TCI device to predict the effect compartment and showed the value of targeting the effect compartment in achieving clinical effect, *i.e.*, LOR, as predicted by the effect site concentration.

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