

## Effect of Infusion Rate on Thiopental Dose-Response Relationships

### Assessment of a Pharmacokinetic-Pharmacodynamic Model

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**Background:** The rate of administration of an intravenous anesthetic induction agent is an important variable determining the total dose required to reach a given endpoint, such as loss of consciousness (LOC). The influence of infusion rate on the dose-response relationship has not been described rigorously. In this study we characterized the effect of different thiopental infusion rates on the times and doses required to reach a clinical (induction) endpoint.

**Methods:** Fifty-six healthy, nonpremedicated men, aged 19-59 yr, were randomly assigned to receive one of seven different thiopental infusion rates (40, 60, 75, 150, 300, 600, and 1,200 mg/min). The infusion was continued until the patient dropped a held object, indicating LOC. The infusion rates were selected using a simulation which predicted the relationship between the rate of administration and cumulative dose administered at the time of LOC. Average population pharmacokinetic parameters from a three-compartment thiopental model were combined with an effect-site rate constant for thiopental equilibration of  $0.58 \text{ min}^{-1}$  and a median effect-site concentration of 13.8 mg/l from previously published pharmacokinetic and pharmacodynamic models for thiopental. This derived model was used to predict the total amount of thiopental required, at each infusion rate, to produce LOC.

**Results:** The observed median effective doses for infusion rates of 40-150 mg/min were similar and ranged from 296 to 318 mg. Dose requirements increased significantly with increasing infusion rates greater than 150 mg/min; median effective doses for infusion rates of 300, 600, and 1,200 mg/min were significantly different from each other (436, 555, and 711 mg, respectively). The original simulation underestimated the observed thiopental doses at all but the lowest infusion rate. A new simulation was performed using a recently developed combined pharmacokinetic-pharmacodynamic model. This model incorporated a four-compartment thiopental pharmacokinetic model with quantal dose-response data to derive an effect-site rate constant for thiopental equilibration of  $0.29 \text{ min}^{-1}$  and a median effect-site concentration for LOC of 11.3 mg/l. The median thiopental doses predicted by this new simulation under the extreme conditions of a 30-fold range of infusion rates were within 13% of the observed doses.

**Conclusions:** In this study we quantified the relationship between the rate of thiopental administration and the resultant cumulative thiopental dose necessary to produce LOC. This study validated a novel pharmacokinetic-pharmacodynamic model based on a four-compartment pharmacokinetic model and infusion quantal dose-response data. Finally, we demonstrated that thiopental dose-response relationships are dependent on drug administration rate, and found that the ability to predict this dependence accurately is influenced by the pharmacokinetics, pharmacodynamics, and median effect-site concentration used to simulate the dose-response relationships. (Key words: Anesthetics, intravenous: thiopental. Pharmacodynamics: infusion rate. Pharmacokinetics.)

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THE rate of administration of an intravenously administered anesthetic induction agent is an important variable determining the total dose administered when the infusion is continued until a given endpoint is observed. Previous studies have reported that, when a drug is administered at rapid infusion rates, larger total doses result and shorter induction times are required than when the drug is administered at slower infusion rates.<sup>1,2</sup> These observations suggest the relationship between cumulative dose and infusion rate is a simple linear relationship (*i.e.*, continuously increasing doses

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with increasing infusion rates), but basic pharmacokinetic principles suggest it should not be. The lowest theoretically effective infusion rate should also require a very large dose because the plasma concentration will asymptotically approach the target (the median effect-site concentration required to result in a given endpoint over time [ $EC_{50}$ ]) when the rate of drug administration equals the product of the target concentration and the elimination clearance<sup>3</sup>; more rapid infusion rates will result in lower cumulative doses required to reach a given endpoint until an infusion rate is reached beyond which this relationship reverses, and doses again increase.<sup>1,2</sup> Thus, the largest dose requirements resulting in a given endpoint should be observed at extremely rapid and extremely slow administration rates with lesser doses observed at intermediate rates. The relationship between infusion rate and the dose required to obtain a given effect of a rapidly acting intravenous anesthetic has not been described rigorously.

Combined pharmacokinetic-pharmacodynamic models are useful for determining the influence of administration, disposition, and effect variables (*e.g.*, target effect-site concentration) on dose-response relationships. These models can be used to predict the time-course and intensity of drug effect when the drug is infused at various rates.

The purpose of the present study was to characterize the relationship between thiopental administration rates and the resultant total doses required to reach loss of consciousness (LOC) in a clinical study. The infusion rates were chosen to examine this relationship over a range of infusion rates beyond those used in previously reported studies and to result in clinically acceptable induction times.

## Materials and Methods

### Clinical Study

Fifty-six ASA physical status 1 or 2 men, aged 19–59 yr and scheduled for elective surgery requiring general anesthesia participated in this institutionally-approved study after giving their written informed consent. Patients chronically using central nervous system active drugs (*e.g.*, anticonvulsants, tricyclic antidepressants, or controlled substances) were excluded from the study as were patients receiving either benzodiazepines or opiates acutely (as either a sleeping pill the evening before the study or as a preanesthetic sedative on the day of the study). Patients with symptomatic gastro-

esophageal reflux or hiatal hernias were also excluded from the study. Patients unable to complete the described protocol for any reason (*e.g.*, equipment failure) were dropped from the study and replaced.

Patients were allowed nothing by mouth from midnight the night before surgery. Age, race, and ASA physical status were recorded. Height and body weight were determined by the investigators on the day of the study. A large bore catheter was inserted into a proximal arm vein of the nondominant arm, and 300–500 ml of a crystalloid solution were infused before initiating the study.

The patient was then taken to the operating room where an attending anesthesiologist not involved in the conduct of the study took responsibility for the care of the patient. Supplemental oxygen was administered at the discretion of that anesthesiologist. Routine monitors were applied and the blood pressure and heart rate were measured frequently and recorded. The patient was asked to hold a 20 ml, water-filled plastic syringe barrel between the thumb and index finger of the dominant hand, a task requiring a conscious response.<sup>4</sup> This arm was supported at the elbow, and the forearm was placed approximately at a 45° angle above the horizontal to the side of the operating table.

The patients were randomly assigned, using computer generated random numbers, to receive one of seven different infusion rates of thiopental. To select the infusion rates to be studied, we simulated the relationship between thiopental infusion rate and the cumulative dose necessary to produce LOC. We simulated the relationship of thiopental infusion rate *versus* dose at LOC using the interactive, direct-executing dynamic system software DESIRE,<sup>5</sup> implemented on an 80386/387 IBM-compatible computer (Northgate Computer Systems, Eden Prairie, MN). Zero-order infusions at rates from 5 to 3,000 mg/min in increments of 5 mg/min, were simulated with the average population pharmacokinetic parameters from Stanski and Maitre's three-compartment thiopental pharmacokinetic model<sup>6</sup> to determine blood concentration histories. These parameters were derived from both bolus and infusion data and included a central volume ( $V_c$ ) of 0.079 l/kg. An effect compartment was modelled using Stanski and Maitre's effect-site rate constant for thiopental equilibration ( $k_{e0}$ ) of 0.58 min<sup>-1</sup> to link the effect with the central compartment drug concentration history. Their  $k_{e0}$  was semiparametrically derived using graded spectral edge thiopental concentration-electroencephalographic (EEG) effect data.<sup>6</sup> The  $EC_{50}$  for loss of verbal response has been reported to be 13.8 mg/l

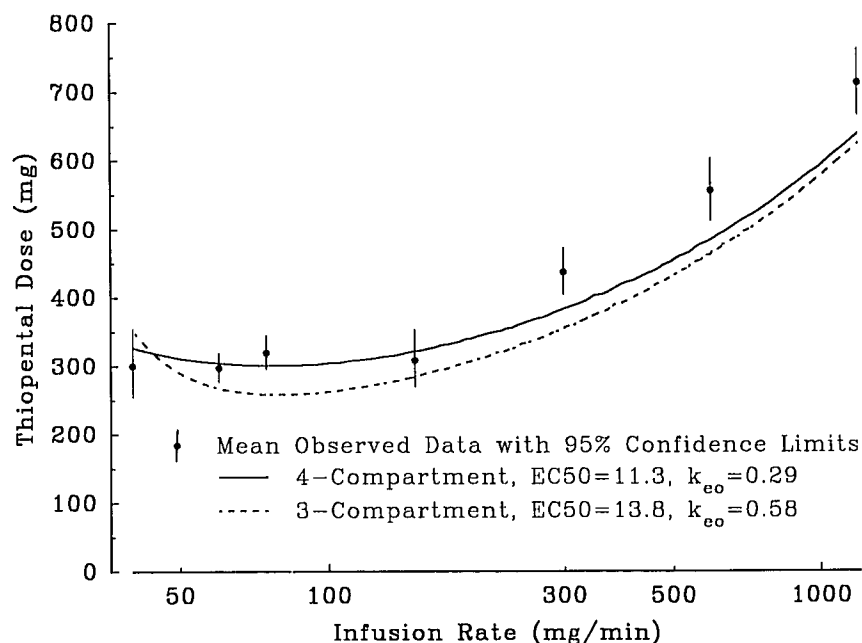


Fig. 1. Simulations of infusion rate *versus* thiopental dose required to produce an  $EC_{50}$  of 13.8 mg/l (three-compartment pharmacokinetic model,  $k_{e0}$  0.58  $\text{min}^{-1}$  [dashed line])<sup>6</sup> and an  $EC_{50}$  of 11.3 mg/l (four-compartment pharmacokinetic model,  $k_{e0}$  0.29  $\text{min}^{-1}$  [solid line]).<sup>11</sup> The observed doses from the clinical study at each rate (filled circles) are shown with their 95% confidence intervals.

by Hung *et al.*<sup>7</sup> The cumulative dose estimated to reach this  $EC_{50}$ , when the infusion was continued until this  $EC_{50}$  was obtained, was determined at each infusion rate (fig. 1).

Infusion rates of 40, 60, 75, 150, 300, 600, and 1,200 mg/min were selected to describe the curve of dose *versus* infusion rate defined by the simulation described above (fig. 1). The infusion was administered using a calibrated syringe pump (Syringe Infusion Pump 22, Harvard Apparatus, Southwick, MA). Anesthesia was induced by infusing a freshly prepared 2.5% thiopental sodium solution at the selected rate into an infusion port 18 cm from the hub of the intravenous catheter while the crystalloid solution was running at approximately 300 ml/min. The thiopental infusion was continued until the patient dropped the syringe barrel, indicating LOC. This endpoint was chosen because it allowed continuous assessment of a clinical endpoint and a clear determination of that endpoint, free from observer bias and without stimulation to elicit patient response.<sup>4</sup> At the time of LOC, the lungs were ventilated with 100% oxygen, and anesthesia was continued as appropriate. The dose at the moment of LOC was calculated as the product of the time (15-min maximum) taken to reach syringe drop and the calibrated infusion rate. If the patient did not drop the syringe barrel within 15 min of the start of the infusion, the infusion was stopped and, to complete induction,

a bolus of thiopental or other induction agent was administered at the discretion of the attending anesthesiologist.

Interval data were expressed as mean and standard deviation. ASA physical status differences were evaluated across all infusion groups using the Kruskal-Wallis statistic.<sup>8</sup> Other demographic variables of patients in each infusion rate group were compared using a one-way analysis of variance. *Post hoc* analysis using the Bonferroni correction of the Student's *t* test would have been done had differences been found.<sup>8</sup> The criterion for rejection of the null hypothesis was  $P < 0.05$ .

Quantal dose-response relationships for the clinical endpoint were obtained for the patients at each infusion rate using linear regression analysis after log-probit transformation.<sup>9</sup> Relative potencies of all infusion rates were estimated as a ratio of median effective doses ( $ED_{50}$ s); 95% confidence intervals for each  $ED_{50}$  and for the ratios of individual  $ED_{50}$ s (*i.e.*, relative potency) were determined with a Litchfield-Wilcoxon analysis program.<sup>10</sup> Potency was considered to be different when the 95% confidence interval for the relative potency did not include 1.0.

#### Pharmacokinetic-Pharmacodynamic Reassessment

We evaluated a new combined pharmacokinetic-pharmacodynamic model developed after completion

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of this clinical study by Shanks *et al.*<sup>11</sup> using the pharmacokinetic and pharmacodynamic parameters from this new model to simulate the relationship of infusion rate *versus* dose. This model used the population mean pharmacokinetic parameters derived from our bolus thiopental pharmacokinetic study in which the disposition of thiopental was described using a *four*-compartment open mamillary model, with a central volume of 3.20 l,<sup>12</sup> combined with *quantal* data from our infusion dose-response study.<sup>13</sup>

Both of our previous studies<sup>12,13</sup> included healthy male surgical patients aged 20–80 yr. In the pharmacokinetic study,<sup>12</sup> the patients received thiopental, 3 mg/kg, as a bolus over 15 s *via* a peripheral venous catheter for induction of anesthesia. Frequent arterial blood sampling resulted in concentration-time data which were best characterized by a four-compartment open mamillary model incorporating late intravascular mixing. These data were used to estimate population parameters determined by entering the individual covariance matrices into the population mean subroutine of the SAAM30.1/CONSAM<sup>14,15</sup> program to derive a mean covariance matrix and population mean pharmacokinetic parameters.

In the infusion dose-response study,<sup>13</sup> thiopental was administered at a constant rate of 150 mg/min until the patient both dropped a syringe (the same clinical endpoint used in the present study)<sup>4</sup> and, subsequently, 3–5 s of EEG isoelectricity was noted (the EEG endpoint).<sup>16</sup> A separate population or cumulative frequency quantal dose-response relationship was generated for the clinical endpoint and for the EEG endpoint.

In the paper by Shanks *et al.*,<sup>11</sup> the response-time data for both the clinical endpoint and the EEG endpoint of the infusion dose-response study<sup>13</sup> were linked with an input function consisting of the convolution of the population mean four-compartment model of the pharmacokinetic study<sup>12</sup> and a 150-mg/min zero-order input, using a common biophase. The resultant pharmacokinetic-pharmacodynamic model characterized simultaneously the infusion concentration-time curve and the two response-time data sets. The drug concentration-time data and mean response-time data sets were analyzed with the SAAM30.1/CONSAM program<sup>14,15</sup> implemented on a 80386/387 IBM compatible personal computer (Northgate Computer Systems, Eden Prairie, MN). The data were found to be represented best by a single  $k_{e0}$  of 0.29 min<sup>-1</sup>. The EC<sub>50</sub>s resulting in LOC and

**Table 1. Patient Characteristics**

Infusion Rate Group (mg/min)	ASA PS* 1/2	Age (yr)	Weight (kg)	Height (cm)
40	8/0	30 ± 6	76 ± 13	180 ± 8
60	5/3	41 ± 6	72 ± 15	174 ± 7
75	6/2	39 ± 8	90 ± 11	181 ± 6
150	7/1	38 ± 14	87 ± 13	178 ± 8
300	8/0	36 ± 4	88 ± 9	182 ± 6
600	8/0	37 ± 13	84 ± 15	180 ± 6
1,200	6/2	36 ± 12	87 ± 16	179 ± 9

Values are mean ± SD.

\* Only ASA physical status 1 and 2 male patients were included in this study.

EEG burst suppression were determined to be 11.3 and 33.9 mg/l, respectively.<sup>11</sup>

## Results

Characteristics of the 56 male patients who participated in this study are presented in table 1. There were no significant differences in ASA physical status, age, height, weight, or race among the infusion rate groups.

LOC did not occur during the allotted 15-min infusion in only one patient. This patient was in the 40-mg/min group and was assigned the maximum induction dose of 600 mg (40 mg/min × 15 min).

The observed ED<sub>50</sub>s for infusion rates of 40, 60, 75, and 150 mg/min were not significantly different and ranged from 296 to 318 mg (fig. 1). Dose requirements increased significantly with increasing infusion rates greater than 150 mg/min; ED<sub>50</sub>s for infusion rates of 300, 600, and 1,200 mg/min were significantly different from those at lower infusion rates and from each other (436, 555, and 711 mg, respectively) (fig. 1).

The original simulation consistently underestimated the observed thiopental doses at all infusion rates except the 40-mg/min rate. The simulation based on a recent pharmacokinetic-pharmacodynamic model<sup>11</sup> accurately predicted median thiopental doses under the extreme conditions of a 30-fold range of infusion rates (fig. 1). There was, however, a slight systematic error (<13% underestimation) in the predictions by this model at the higher infusion rates.

## Discussion

In this study we described thiopental dose-response relationships at various administration rates. We found

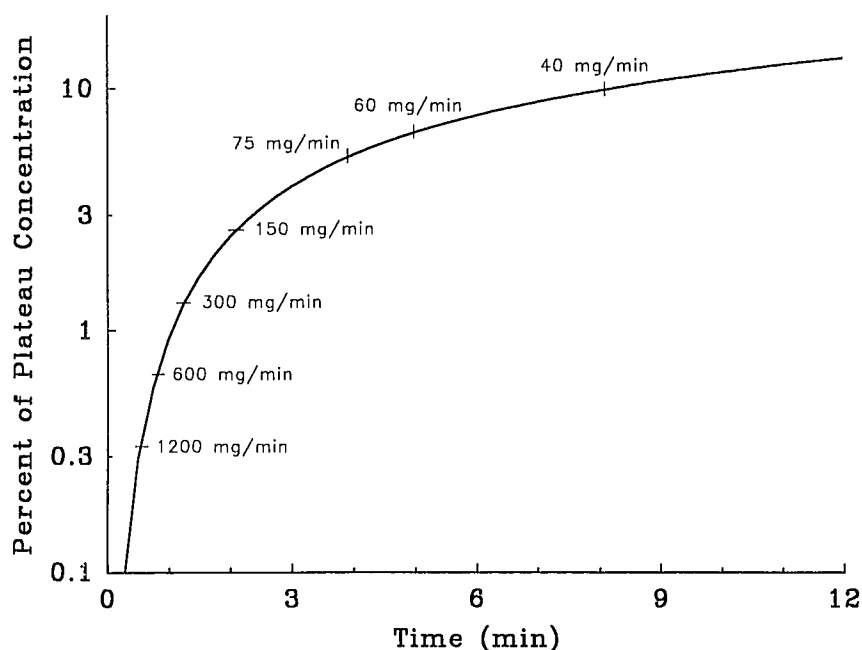


Fig. 2. Simulations of effect-site concentration *versus* duration of infusion (time) with continuous infusion using a four-compartment model and a  $k_{e0}$  of  $0.29 \text{ min}^{-1}$ .<sup>11</sup> The eventual effect-site steady-state concentration is normalized to 100% (y axis truncated to 20%) and the percentage of the eventual steady-state concentration (plateau) at which each of the seven infusion rates used in this study results in an  $EC_{50}$  of 11.3 mg/l is noted on the curve. For example, an infusion duration of 8.1 min at a rate of 40 mg/min would be predicted to reach 9.9% ( $EC_{50}$  11.3 mg/l) of the eventual plateau concentration (114 mg/l).

that when infusions of thiopental were continued until patients lost consciousness, the dose-response relationships were similar at infusion rates from 40 to 150 mg/min, but significantly higher doses were administered at more rapid infusion rates (300, 600, and 1,200 mg/min). We also found that the relationship of cumulative thiopental dose *versus* infusion rate is *not* a simple linear relationship; when administered to a syringe drop endpoint, thiopental doses were *not* different when infused at rates from 40–150 mg/min. This study validated the combined pharmacokinetic-pharmacodynamic model we developed recently<sup>11</sup>; a simulation using data from this model accurately (within 13%) predicted doses at LOC over a 30-fold range of infusion rates (fig. 1).

Both of the simulations used in this study allowed reasonable predictions of the relationship of thiopental dose *versus* infusion rate, and both predicted that, in the infusion rate range studied, this relationship would *not* be a simple linear relationship. We selected our lowest infusion rate (40 mg/min) based on the original simulation, using a three-compartment pharmacokinetic model for thiopental with a  $k_{e0}$  of  $0.58 \text{ min}^{-1}$  and  $EC_{50}$  of 13.8 mg/l.<sup>7</sup> This original simulation (fig. 1) predicted that the cumulative dose requirement at 40 mg/min would be 37% larger than that observed at the 75-mg/min infusion rate (353 *vs.* 258 mg, respectively). The new simulation, which uses a four-com-

partment pharmacokinetic model, a  $k_{e0}$  of  $0.29 \text{ min}^{-1}$ , and an  $EC_{50}$  of 11.3 mg/l, (fig. 1) successfully predicted (within 10%) the observed doses at the low infusion rates and predicted that doses resulting in LOC would not be different from 40 to 75 mg/min (327 *vs.* 301 mg, respectively, a difference of <9%). The new model predicted that larger doses would be required only at infusion rates of 20 mg/min or lower. Infusion rates this low would result in induction times far longer than would be *clinically* acceptable; at 10 mg/min, the new combined model predicts that an infusion at this rate for 74 min or longer ( $ED_{50}$  of 737 mg) would be required to produce LOC in one-half of the subjects.

For linear multicompartmental models, the increase in plasma and effect-site concentrations during a constant rate infusion is a complex function that is best understood by simulation. Like the simple one-compartment model, a steady-state is eventually reached at a concentration equal to the infusion rate divided by the elimination clearance, but the attainment of any fraction of this steady-state concentration cannot be expressed in terms of multiples of half-lives or time constants as it can for the one-compartment model. A graphic representation of the increase in effect-site concentrations toward steady-state during constant rate infusions for the four-compartment model is shown in figure 2. If the eventual steady-state concentration is normalized to 100%, then the time that any fraction of

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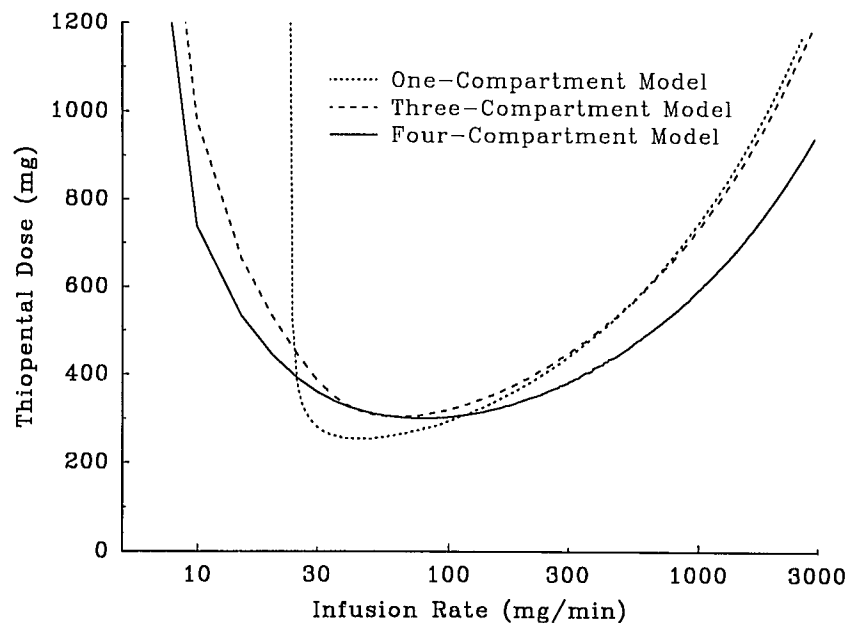


Fig. 3. Simulations of infusion rate *versus* thiopental dose. The thiopental dose calculated to result in an  $EC_{50}$  of 11.3 mg/l using a  $k_{e0}$  of  $0.29 \text{ min}^{-1}$  and three different pharmacokinetic models is shown (one-compartment model [dotted line],<sup>6</sup> three-compartment model [dashed line],<sup>6</sup> and four-compartment model [solid line].<sup>12</sup>).

steady-state is reached can be discerned. For this model, an infusion of 1,200 mg/min would theoretically result in an impressive steady-state concentration of 3,428 mg/l, or 303 times the target concentration of 11.3 mg/l. With all the infusion rates plotted in this manner in figure 2, it can be seen that fast infusion rates can be defined as those that attain the target concentration on the initial, rapidly rising portion of the curve and slow infusion rates are those that attain the target concentration on the plateau of the curve. These positions have different implications for the time to onset of effect.

When target concentrations are attained during the early rapid increase in plasma concentrations observed immediately after initiation of an infusion, the infusion rate is high by definition and will produce the desired effect after a short duration of that infusion (fig. 2; *e.g.*, 1,200 mg/min). Both of the simulations used in this study systematically underestimated the doses required at the greater infusion rates (fig. 1). One possible explanation for this is that both of the traditional pharmacokinetic models make the assumption that all compartments are continuous and that drug administered into or transferred to a compartment mixes instantaneously within it.<sup>17</sup> In reality, the compartments are discontinuous, separated by circulation delays.<sup>18,19</sup> A circulation delay (*e.g.*, vein-to-brain circulation time) is the time necessary to transfer drug between compartments and results in noninstantaneous drug transfer

to tissues.<sup>18,19</sup> These circulation delays, which are not incorporated in conventional compartmental models, become increasingly important as drug reservoirs at higher infusion rates, in effect temporarily removing drug from the model. Thus, a smaller dose is predicted than was actually administered at the time of LOC at high infusion rates. A recirculatory compartmental model has been developed for indocyanine green (ICG) which accounts for the circulation delays and could be used to describe more accurately the intravascular kinetics of drugs such as thiopental,<sup>18,19</sup> improving dose predictability at high infusion rates.

The increase and decrease of the effect-site concentration, and thus the degree of dissociation between the central compartment concentration and the effect-site concentration, is the convolution of the drug concentration history of the central compartment and the effect-site unit disposition function. The effect-site unit disposition for a given pharmacodynamic model changes only with changes in  $k_{e0}$ . Thus, predictions of the dose required to reach a given target effect-site concentration using combined pharmacokinetic-pharmacodynamic models are dependent on the rate of administration of the drug, the pharmacokinetic model describing the concentration history of the central compartment, the  $k_{e0}$  describing the dissociation between the plasma and the effect compartment, and the  $EC_{50}$ . The two sets of variables used in this study to perform the simulations differed with respect to

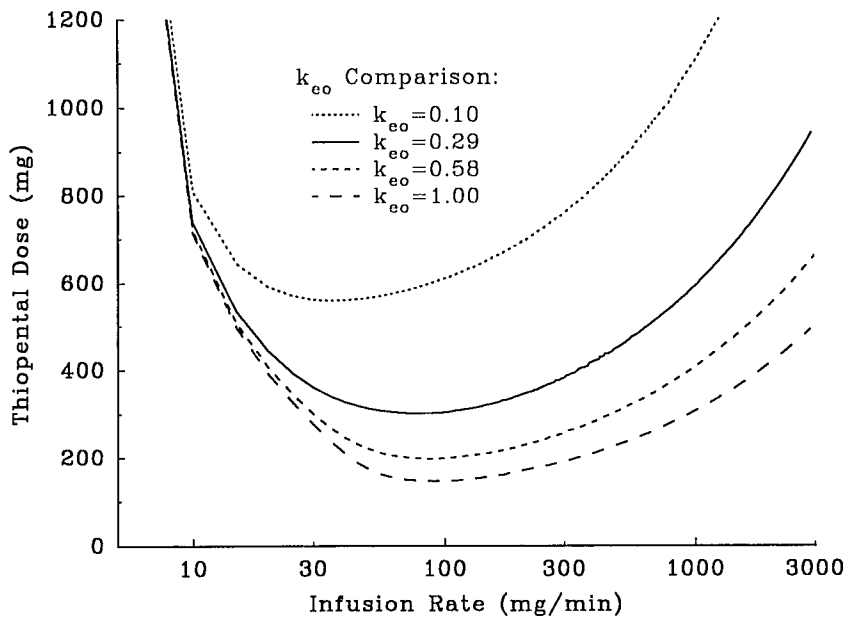


Fig. 4. Simulations of infusion rate *versus* thiopental dose. The thiopental dose calculated to result in an  $EC_{50}$  of 11.3 mg/l using a four-compartment model and four  $k_{e0}$ s is shown ( $k_{e0}$  0.10  $\text{min}^{-1}$  [dotted line],  $k_{e0}$  0.29  $\text{min}^{-1}$  [solid line],  $k_{e0}$  0.58  $\text{min}^{-1}$  [dashed line], and  $k_{e0}$  1.0  $\text{min}^{-1}$  [long dashes]).

pharmacokinetic model,  $k_{e0}$ , and  $EC_{50}$ . We analyzed the influence of each of these variables on the relationship of infusion rate *versus* thiopental dose–response using simulations.

The effect-site concentration history for a given  $k_{e0}$  will be determined by the plasma concentration history predicted by the pharmacokinetic model. Figure 3 shows the effect of changing the pharmacokinetic model on the relationship of infusion rate *versus* dose for the syringe drop endpoint. When target concentrations are near the steady-state concentration for an infusion rate (*i.e.*, steady-state concentration = infusion rate/elimination clearance), the infusion rate is low by definition and will produce the desired target concentration only after a prolonged infusion duration. The target concentration is attained near the plateau phase of the curve of effect-site concentration *versus* time (fig. 2; *e.g.*, 40 mg/min). The slow increases in the central compartment and effect-site concentrations as the target concentration is approached during slow infusions result in nearly simultaneous peak concentrations in these compartments. The prolonged infusion duration required to reach the target concentration results in the loss of a significant amount of drug as a result of redistribution and elimination, increasing the dose required at these low rates. Because the one-compartment model treats intercompartmental clearance as elimination clearance, it overestimates drug loss and

misspecifies dose requirements at low infusion rates (fig. 3). At greater infusion rates, the volume of the central compartment is more important in estimating the dose needed to produce the desired effect than is clearance of drug from the central compartment; the larger dose predictions of the one- and three-compartment models at infusion rates greater than 150 mg/min required to reach LOC reflect the longer equilibration times and greater dilution capacity of the larger central volumes (6.07 and 5.53 l, respectively) compared with that of the four-compartment model (3.20 l).

The rate constant quantifying the temporal dissociation between the plasma (central compartment) concentrations and effect is  $k_{e0}$ . For a given pharmacokinetic model, a larger  $k_{e0}$  implies more rapid equilibration (*i.e.*, less temporal dissociation) between the plasma concentrations and the apparent effect-site concentrations, whereas smaller  $k_{e0}$  values imply slower equilibration (*i.e.*, more temporal dissociation).<sup>20</sup> Figure 4 shows the result of changing the  $k_{e0}$  on the relationship of infusion rate *versus* dose. When the central compartment concentration history is maintained and  $k_{e0}$  is varied, the doses estimated to reach a given endpoint differ with changes in degree of dissociation between the plasma concentration and effect. At lower infusion rates, biophase equilibration time and circulation delays are small compared with

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the time required to reach the central compartment concentration which will result in the targeted effect compartment concentration; the disparity between the doses predicted for a given endpoint is minimal for the same pharmacokinetic model and  $EC_{50}$  but different  $k_{e0}$ s at low infusion rates. At higher infusion rates, the plasma concentration rises more rapidly than does the effect-site concentration, and circulation delays and effect-site/plasma equilibration times become determinants of the estimated dose. A consequence of the bi-phase equilibration time- and circulation delay-determined dose is the administration of excess drug at the time of the observed endpoint. These larger doses result in quicker onset and increased duration of the drug effect.

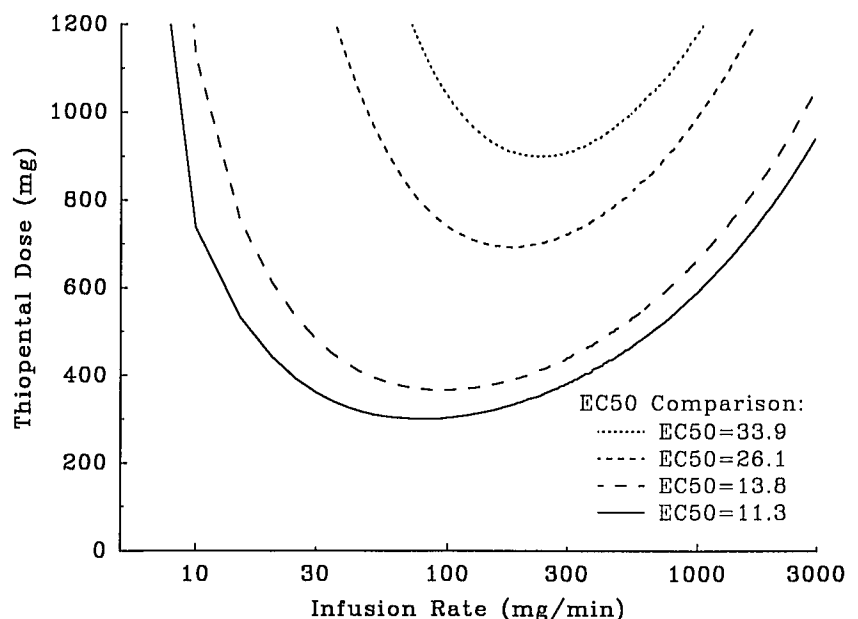
For a given pharmacokinetic-pharmacodynamic model, the relationship of infusion rate *versus* dose is a function of the target concentration. The nonlinearity of this relationship (fig. 5) indicates that  $EC_{50}$  is not a simple scaling factor. When a drug is administered until a target effect concentration is reached, the predicted doses and durations of infusion increase with increasing target  $EC_{50}$  for a given infusion rate. The lowest theoretically effective infusion rate also increases with increasing target concentration because this infusion rate is the product of the elimination clearance and the  $EC_{50}$ .

The  $EC_{50}$  of 13.8 mg/l for loss of verbal response<sup>7</sup> was chosen as the endpoint for the original simulations

because it was the available value felt to best represent the endpoint used in this study. This target concentration may be too high. Like the loss of verbal responsiveness endpoint, the syringe drop endpoint ( $EC_{50}$  11.3 mg/l) represents LOC because holding an object requires a continuous conscious response.<sup>4</sup> However, the syringe drop endpoint also provides a more accurate determination of LOC than does loss of verbal response because it does not depend on frequency of observer intervention.

The differences in the  $k_{e0}$ s derived by Stanski and Maitre<sup>6</sup> and Shanks *et al.*<sup>11</sup> may lie in the endpoints studied in each of the pharmacodynamic studies. Both authors used similar plasma thiopental concentration data collected during the time of thiopental peak effect, and both used the Hill sigmoid  $E_{max}$  (median effect-site concentration at maximum effect) equation to describe their concentration-effect relationships. The pharmacodynamic endpoints used in the two studies differed markedly. Stanski and Maitre used continuously collected *graded* EEG spectral edge data,<sup>6</sup> whereas Shanks *et al.* used continuously collected clinical and EEG data to the *quantal* endpoints of syringe drop and burst suppression of the raw EEG waveform.<sup>11,13</sup> The use of the graded EEG spectral edge measurement to characterize the thiopental plasma concentration-effect relationship in the study by Stanski and Maitre<sup>6</sup> has been questioned recently that group because the spectral edge parameter becomes unstable as the EEG nears

Fig. 5. Simulations of infusion rate *versus* thiopental dose. The thiopental dose calculated to result in four  $EC_{50}$ s using a  $k_{e0}$  of 0.29 mg/l and a four-compartment pharmacokinetic model is shown ( $EC_{50}$  33.9 mg/l [EEG burst suppression<sup>11</sup>] [dotted line],  $EC_{50}$  26.1 mg/l [loss of corneal reflex<sup>11</sup>] [dashed line],  $EC_{50}$  13.8 mg/l [loss of verbal response<sup>7</sup>] [long dashes], and  $EC_{50}$  of 11.3 mg/l [syringe drop<sup>11</sup>] [solid line]).





burst suppression ( $E_{\max}$ ),<sup>21</sup> and pharmacodynamic modeling of the spectral edge did not incorporate EEG activation at low concentrations.<sup>22</sup> Although accurate characterization of  $E_{\max}$  is not necessary for  $k_{c0}$  determination, accurate characterization of the thiopental plasma concentration–effect relationship is essential when determining  $k_{c0}$ . Characterization of the thiopental concentration–effect relationship did not present the same problems in the Shanks *et al.* study because this pharmacodynamic endpoint represented the cumulative population response at the quantal endpoints.

In conclusion, numerous factors determine the cumulative dose of thiopental required to produce LOC including the drug administration rate. The pharmacokinetic model,  $k_{c0}$ , and  $EC_{50}$  all are important in predicting effective doses of thiopental using combined pharmacokinetic–pharmacodynamic models. We also demonstrated that there is a complex relationship among  $k_{c0}$ ,  $EC_{50}$ , pharmacokinetic models, and dosing regimens when simulating or predicting the dose–response relationship. Therefore, when estimating dose requirement, these factors are best applied with knowledge of the pharmacokinetics and pharmacodynamics used in their derivation.

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