

Using Front-end Kinetics to Optimize Target-controlled Drug Infusions

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Background: The mode of drug administration, blood sampling schedule, and sampling site affect the pharmacokinetic model derived. The present study tested the hypothesis that three-compartment pharmacokinetic model parameters derived from arterial drug concentrations obtained after rapid intravenous administration can be used to design a target-controlled drug infusion (TCI) that deviates minimally from the target.

Methods: Arterial thiopental concentration data obtained from the moment of injection in a previous study of five dogs were used. Three three-compartment models were constructed, one based on early concentrations classically obtained at 1, 2, and 3 min; another using all concentrations obtained beginning with the thiopental recirculation peak; and the last with the initial distribution volume (V_c) fixed to the sum of V_c and the nondistributive volume of the recirculatory model from the earlier study. Using these models, TCIs were designed that would maintain 20 $\mu\text{g/ml}$ thiopental concentrations in V_c for 60 min if simulated with the models used in their design. Drug concentrations resulting from these TCIs were then simulated using recirculatory model kinetics, and prediction errors were evaluated.

Results: Models with V_c s estimated from intermittent or frequent early blood concentrations overestimated not only V_c but also the volume and clearance of the rapidly equilibrating tissues, and their TCIs significantly overshoot the target. With V_c fixed to recirculatory model parameters, drug distribution was described in a manner consistent with that of the recirculatory model, and the TCI deviated minimally from the target. A similar three-compartment model was derived from data obtained from a simulation of a 2-min infusion using recirculatory kinetic parameters.

Conclusions: Because three-compartment models based on drug concentration histories obtained after rapid intravenous administration do not characterize V_c accurately, TCIs based on them produce concentrations exceeding the target. A model capable of producing TCIs deviating minimally from the target

can be derived from data obtained during and after a brief drug infusion.

EARLY drug distribution kinetics (front-end kinetics) determine the rate and extent of both drug distribution to the brain and its dilution by distribution to indifferent tissues.¹ Both cardiac output and its peripheral distribution are important determinants of the early drug concentration-*versus*-time relation of intravenously administered drugs and interindividual variability in response to rapidly acting intravenous anesthetics. The purpose of the current study is to illustrate the importance of accurate characterization of front-end kinetics to the optimal design of target-controlled drug infusions.

Traditional pharmacokinetic models (fig. 1) are based on the simplifying assumption that intravenously administered drugs mix instantaneously and completely within an initial distribution volume (central volume, V_c) that includes, at a minimum, intravascular space.² In reality, the volume of distribution of a drug expands with a time course dependent on the physiologic environment and the chemical characteristics of the drug.³⁻⁵ As a result, the earlier one obtains blood samples after rapid intravenous drug administration, and the smaller will be the estimate of V_c .^{6,7} Nonetheless, conventional pharmacokinetic models overestimate V_c because they ignore the complexity of intravascular mixing.⁸ When pharmacokinetic models in which V_c is overestimated are used to design target-controlled intravenous drug infusions, drug concentrations not only greatly exceed the target concentration in the first minutes after commencing the infusion but may also significantly exceed it long after starting the infusion.⁹

We have developed a recirculatory multicompartamental pharmacokinetic model that describes drug disposition from the moment of rapid intravenous injection (fig. 2).¹⁰⁻¹² This model addresses Chiou's concerns about traditional mammillary multicompartamental analysis.^{13,14} In the fit of the recirculatory model to the data, the concentration at time zero is zero, and there is a delay between the time drug is administered and the time drug appears at the sampling site. The model fits the early arterial drug concentrations of samples obtained frequently soon after rapid intravenous input that resemble the drug concentration profiles resulting from a zero-order intravenous infusion. Pulmonary drug uptake is an integral part of the model.¹⁵ Intravascular mixing is characterized by the recirculatory model, as is the role of cardiac output in drug distribution. Finally, arterial-ve-

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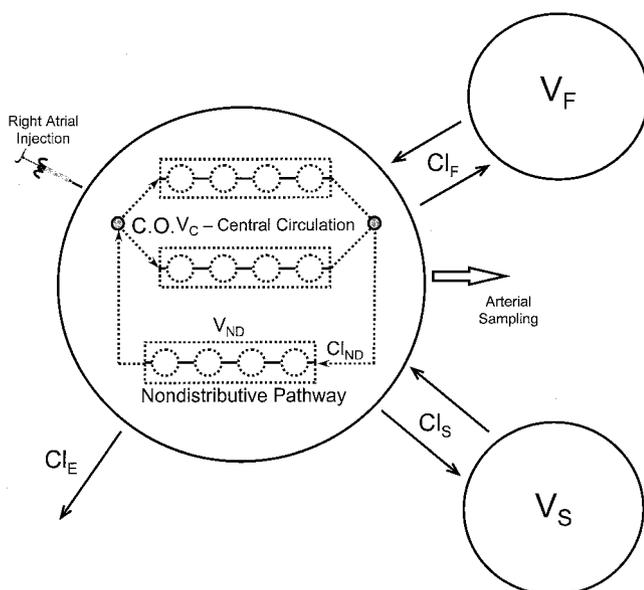


Fig. 1. In a three-compartment pharmacokinetic model, the central or initial volume of distribution (V_C) is that volume in which a drug appears to mix instantaneously before distribution throughout the remaining apparent volume of distribution. The ideal V_C includes only the central circulation and nondistributive peripheral pathway(s) of the recirculatory pharmacokinetic model (fig. 2). From V_C , drug is distributed to the rapidly (fast) and slowly equilibrating volumes of distribution (V_F and V_S , respectively) by intercompartmental clearance (Cl_I). Intercompartmental clearances between V_C and both V_F and V_S (Cl_F and Cl_S , respectively) are volume-independent estimates of drug transfer that are determined by blood flow and transcappillary permeability. The volume of distribution at steady state (V_{SS}) is the total volume of distribution and, as such, is the sum of V_C , V_F , and V_S . Elimination clearance (Cl_E) quantifies the irreversible removal of drug from the body or drug metabolism. CO = cardiac output; ND = nondistributive.

nous concentration differences are accounted for by the model.¹⁶ The underlying assumption of the current study is that the concentrations predicted by simulations using the recirculatory pharmacokinetic model are a very close approximation of reality.

Although the recirculatory model may be considered an accurate description of drug disposition from the moment of injection, it is based on data collected during technically demanding experiments and requires complex modeling of at least two concomitantly administered markers. These requirements make it unsuitable for routine application to pharmacokinetic studies being conducted to derive pharmacokinetic parameters that can be used to design accurate target-controlled drug infusions. Therefore, it is desirable to identify a more convenient experimental design and more facile data analysis that would result in the development of a three-compartment mammillary pharmacokinetic model that is consistent with the recirculatory model. To that end, we sought to determine whether it is possible to obtain arterial blood samples early enough after rapid intravenous drug administration to develop a three-compartment model with a V_C that is small enough that periph-

eral drug distribution is characterized in a manner consistent with its description by the recirculatory model. Failing that, we sought to identify another experimental design that would yield data that would result in the development of such a model.

The current study tested the hypothesis that three-compartment pharmacokinetic models based on drug concentration histories obtained beginning soon after rapid intravenous drug administration would differ from recirculatory kinetic models only in their description of V_C . In addition, we tested the hypothesis that three-compartment pharmacokinetic models based on drug concentration histories obtained after rapid intravenous drug administration can be used to design target-controlled drug infusions that produce drug concentrations deviating minimally from the target concentration.

Materials and Methods

Experimental Protocol

Five male dogs, weighing 32–42.3 kg (36.7 ± 4.6 kg), were studied in this Institutional Animal Care and Use Committee-approved study, details of which have been reported previously¹⁷ and are summarized briefly.

Anesthesia was induced with ketamine (5 mg/kg intravenously) and maintained with halothane (1.5% in oxygen) administered *via* an endotracheal tube. The study was begun when the dog was hemodynamically stable. Indocyanine green (ICG; Cardio-Green[®]; Becton Dickinson, Cockeysville, MD), 5 mg in 1 ml ICG diluent, and thiopental (Abbott Laboratories, North Chicago, IL), 100 mg in 2 ml diluent, were placed sequentially in an intravenous tubing and connected to the proximal injection port of a flow-directed thermal dilution pulmonary artery catheter that had been inserted through a right external jugular vein sheath introducer. At the onset of the study (time $t = 0$ min), the drug volume was flushed into the right atrium within 4 s using 10 ml of a 0.9% saline solution, allowing simultaneous determination of dye and thermal dilution cardiac outputs. Thirty arterial blood samples were collected *via* an implanted Vascular-Access-Port (Access Technologies, Skokie, IL)¹⁸ every 0.05 min for the first minute and every 0.1 min for the next minute using a computer-controlled roller pump (Masterflex; Cole-Parmer, Chicago, IL). Subsequently, 30 more 3-ml arterial blood samples were drawn manually at 0.5-min intervals to 4 min, at 5 and 6 min, every 2 min to 20 min, every 5 min to 30 min, every 10 min to 60 min, every 15 min to 90 min, every half hour to 3 h, and every hour to 10 h.

Analytic Methods

Plasma ICG concentrations of all samples obtained up to 20 min were measured on the study day by the high-performance liquid chromatographic technique of

Grasela *et al.*¹⁹ as modified in our laboratory.¹⁰ Plasma thiopental concentrations were measured within 24 h of sample collection using a high-performance liquid chromatographic technique developed in our laboratory.²⁰ To interpret intercompartmental clearances in relation to blood flow, the recirculatory models were constructed on the basis of whole blood ICG and thiopental concentrations.

Recirculatory Pharmacokinetic Model

The pharmacokinetic modeling method (fig. 2) has been described in detail previously.^{11,12} It is based on the approach described by Jacquez²¹ for obtaining information from outflow concentration histories, the so-called inverse problem. Thiopental distribution was analyzed as the convolution of its intravascular behavior, determined by the pharmacokinetics of concomitantly administered ICG, and tissue distribution kinetics.¹¹

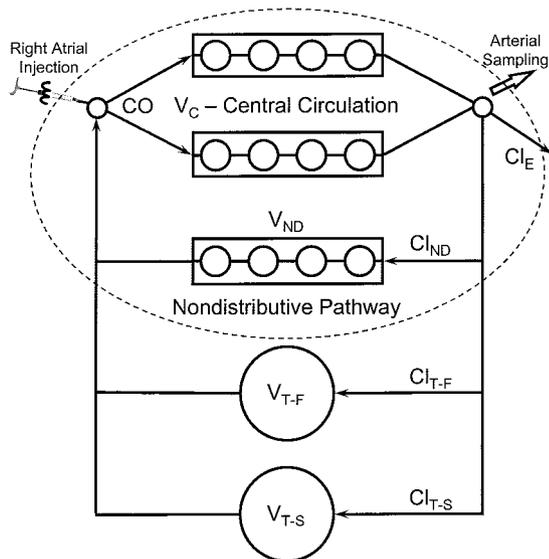


Fig. 2. The general model for the recirculatory pharmacokinetics of indocyanine green and thiopental.¹¹ Cardiac output (CO) flows through the central circulation, which is defined by the delay elements (V_c). All delay elements are represented generically by rectangles surrounding four compartments, although the number of compartments needed in a delay varied between 2 and 30. The pulmonary tissue volume (V_{T-P}), a subset of V_c , is calculated for thiopental by subtracting the V_c of indocyanine green from that of thiopental. Beyond the central circulation, CO distributes to numerous circulatory and tissue pathways which lump, on the basis of their blood volume to flow ratios or tissue volume to distribution clearance ratios (mean transit times), into the volumes (V) and clearances (Cl) of the nondistributive peripheral pathway (V_{ND} , Cl_{ND}) and the fast (V_{T-F} , Cl_{T-F}) and slow (V_{T-S} , Cl_{T-S}) tissue volume groups. The elimination clearances (Cl_E) are modeled from the arterial sampling site without being associated with any particular peripheral circuit. The parallel rapidly and slowly equilibrating tissues are the fast (V_F and Cl_F) and slow (V_S and Cl_S) compartments of traditional three-compartment pharmacokinetic models, respectively, whereas the central circulation and nondistributive peripheral pathway(s) are detailed representations of the ideal central volume (V_c) of the traditional multicompartamental model (fig. 1).²³ Because of the direct correspondence between the recirculatory model and compartmental models, elimination clearance (Cl_E) was modeled from the arterial (sampling) compartment to enable comparison of these results with previous ones.

Arterial ICG and thiopental concentration-*versus*-time data before evidence of recirculation (*i.e.*, first-pass data) were weighted uniformly and fit, independently, to the sum of two Erlang distribution functions using TableCurve2D (version 3.0; SPSS, Chicago, IL) on a Pentium-based personal computer to reflect the heterogeneity in the distribution of transit times in the pulmonary circulation and the pulmonary tissue distribution of thiopental during this time.¹⁵ The thiopental pulmonary tissue volume (V_{T-P}) is the difference between the thiopental central volume (thiopental mean transit time \times cardiac output) and the central intravascular volume determined by ICG (ICG mean transit time \times cardiac output).

In subsequent pharmacokinetic analysis, these descriptions of the central circulation were incorporated as parallel linear chains or delay elements into independent recirculatory models for the individual markers using SAAM II (SAAM Institute, Seattle, WA) implemented on a Pentium-based personal computer.^{15,16} The concentration-time data were weighted, assuming a proportional variance model, in proportion to the inverse of the square of the observed value.²² Systematic deviations of the observed data from the calculated values were sought using the one-tailed one-sample runs test, with $P < 0.05$, corrected for multiple applications of the runs test, as the criterion for rejection of the null hypothesis. Model misspecification was sought by visual inspection of the measured and predicted marker concentration-*versus*-time relations.

In general, peripheral drug distribution can be lumped into identifiable (*i.e.*, mathematically distinct) volumes (V) and clearances (Cl) (fig. 2): nondistributive peripheral pathways (V_{ND} and Cl_{ND}), rapidly (fast) equilibrating tissues (V_{T-F} and Cl_{T-F}), and slowly equilibrating tissues (V_{T-S} and Cl_{T-S}). The single identifiable nondistributive peripheral pathway in the thiopental model (V_{ND} and Cl_{ND}), determined by the recirculation peak, represents blood flow that quickly returns the drug to the central circulation after minimal apparent tissue distribution.^{11,12} In the thiopental model, the parallel rapidly and slowly equilibrating tissues are the fast (V_F and Cl_F) and slow (V_S and Cl_S) compartments of traditional three-compartment pharmacokinetic models, respectively, whereas the central circulation and nondistributive peripheral pathway(s) are detailed representations of the ideal central volume (V_c) of the traditional multicompartamental model (fig. 1).²³ Because of the direct correspondence between the recirculatory model and compartmental models, elimination clearance (Cl_E) was modeled from the arterial (sampling) compartment to enable comparison of these results with previous ones.

Three-compartment Kinetic Models of Data after Rapid Intravenous Drug Administration

The ability of traditional compartmental models to characterize early drug disposition after rapid intrave-

nous drug administration was tested by comparing the parameters of three different three-compartment pharmacokinetic models of thiopental disposition with those of the recirculatory model. Each dog's thiopental concentration-*versus*-time data were fit to three-compartment pharmacokinetic models using SAAM II. The first three-compartment model (model 1) was fit to data collected at 1, 2, and 3 min and all data collected subsequently to emulate a traditional "intense sampling" postbolus sampling schedule. The second three-compartment model (model 2) was fit to all data collected beginning with the thiopental recirculation peak (fig. 3), the highest concentration observed after first pass, to obtain the smallest V_C it is possible to derive from the postbolus data. The central circulation and nondistributive peripheral pathway(s) of the recirculatory model are detailed representations of the ideal central volume of the traditional multicompartmental model.²³ Therefore, the third three-compartment model (model 3) had its V_C fixed to the sum of the corresponding thiopental recirculatory model V_C and V_{ND} and was fit to all data collected beginning with the recirculation peak.

Simulations of Target-controlled Drug Infusions

The descriptions of early drug disposition by the three-compartment models were further evaluated by testing their ability to design error-free target-controlled drug infusions. Each dog's three-compartment pharmacokinetic parameters were used to design infusions that would maintain a constant V_C thiopental concentration of 20 $\mu\text{g/ml}$ for 60 min if simulated with the models used to design them (the BET dosing regimen).²⁴ The thiopental concentrations resulting from infusions based on each dog's three-compartment models were then simulated using the respective dog's recirculatory model. The prediction errors of these simulations were evaluated by calculating the area between the predicted concentration history and the target concentration (20 $\mu\text{g/ml}$) for the duration of the infusion (infusion ΔAUC).

Three-compartment Model Fit to Infusion and Postinfusion Data

The above results clearly indicated that the only three-compartment model based on drug concentration histories obtained after rapid intravenous drug administration that differed from the recirculatory model only in its description of V_C and could be used to produce targeted drug infusions that deviate minimally from the target concentration was the one based retrospectively on the recirculatory model (model 3). Chiou,^{13,14} in his indictment of traditional mammillary multicompartmental analysis, suggested that better estimates of V_C might be obtained from studies in which the drug of interest was administered by a short-term intravenous infusion. Wada and Ward²⁵ used a recirculatory model of alfentanil disposition based on literature values for tissue volumes

and flow fractions to demonstrate the superiority of infusion-derived pharmacokinetic parameters for computer-controlled drug infusions. Therefore, we investigated the possibility that a three-compartment model derived from a short-term infusion study would describe peripheral drug distribution in a manner similar to that of the recirculatory model and could be used to design target-controlled drug infusions with resultant concentrations that deviate minimally from the target.

We thus evaluated a fourth three-compartment model that was based on data obtainable during and after a brief thiopental infusion (model 4). Because infusion-based thiopental concentration-*versus*-time data were not obtained as a part of the study on which the current report is based,¹⁷ data were generated from simulations of 2-min, 30-mg/min thiopental infusions using each dog's recirculatory pharmacokinetic model parameters. Thirty-two predicted arterial thiopental concentrations were obtained every half minute during the 2 min infusion; at 3, 3.5, 4, 5, and 6 min; every 2 min to 20 min; every 5 min to 30 min; every 10 min to 60 min; every 15 min to 90 min; every half hour to 3 h; and every hour to 10 h. Normally distributed random error with a mean error of 0% and an SD of 5% was introduced to the data using the random number generation function in Excel (Microsoft, Seattle, WA). The data were then fit to three-compartment pharmacokinetic models using SAAM II. From these models, target-controlled drug infusions were developed and simulated in the manner described above.

Statistical Analysis

All pharmacokinetic variables were tested by both the Kolmogorov-Smirnov test for a normally distributed population and the Levene median test for equal variance (SigmaStat[®] Statistical Software; SPSS). Data passing these tests were treated as interval and were represented as mean and SD. These data were then compared among models using a one-way repeated-measures analysis of variance with *post hoc* analysis by Tukey multiple comparison test.

Results

The thiopental pharmacokinetic parameters described by the recirculatory model and the four three-compartment models are listed in table 1; the recirculatory model parameters have been reported previously.¹⁷ The blood thiopental concentration-*versus*-time relations of the various data sets were well characterized by the models (fig. 3). Differences in the fits of the models to the data are most apparent in the first 2 min after rapid intravenous drug administration (fig. 3) but are not apparent when the fit to the entire concentration history is examined (fig. 3, *inset*).

Table 1. Pharmacokinetic Parameters for Thiopental in Five Dogs

Model	Volume, l*					Clearance, l/min†					Infusion Δ AUC, $\mu\text{g} \cdot \text{min} \cdot \text{ml}^{-1}\ddagger$
	V_C	V_{ND}	V_F	V_S	V_{SS}	Cl_{ND}	Cl_F	Cl_S	Cl_E	ΣCl	
Recirculatory, based on all bolus data from 0 min on	1.11 (0.28)	0.70 (0.34)	14.26 (7.42)	37.05 (10.76)	53.12 (14.40)	1.18 (0.47)	1.29 (0.49)	0.36 (0.12)	0.17 (0.04)	3.00** (0.89)	7.6 (4.8)
Model 1: Three-compartment, based on 1, 2, 3 min and all subsequent bolus data	3.37§ (1.06)	NA	15.85 (7.79)	38.58 (10.80)	57.80§ (16.16)	NA	2.03§ (0.67)	0.40 (0.14)	0.17 (0.05)	2.60 (0.59)	162.0§ (64.3)
Model 2: Three-compartment, based on all bolus data from recirculatory peak on	3.04§ (1.34)	NA	15.71 (7.79)	38.54 (10.78)	57.29# (15.94)	NA	1.81§ (0.68)	0.38 (0.13)	0.17 (0.05)	2.36†† (0.60)	124.6§ (37.8)
Model 3: Three-compartment, based on bolus data, V_C fixed to recirculatory model	1.80 (0.60)	NA	13.69 (7.34)	38.23 (10.25)	53.73 (14.70)	NA	1.41 (0.53)	0.39 (0.13)	0.17 (0.05)	1.96 (0.47)	17.3 (5.9)
Model 4: Three-compartment, based on simulated 2-min infusion data	1.47 (0.44)	NA	13.70 (8.12)	36.89 (10.42)	52.05 (14.11)	NA	1.28 (0.45)	0.39 (0.15)	0.17 (0.04)	1.83 (0.39)	-3.79 (21.04)

Values are presented as mean (SD).

* The volumes (V) of the central compartment (C), the nondistributive (ND) circuit, and the rapidly equilibrating (fast, F) and slowly equilibrating (S) tissues, and the volume of distribution at steady state (SS), which equals the sum of all volumes. † The clearances (Cl) of the ND circuit and the F and S tissues, elimination clearance (E), and the sum of all clearances (ΣCl), which, in the recirculatory model, equals the indocyanine green (dye dilution) cardiac output determined at the moment of marker injection. ‡ Infusion Δ AUC is the area between the predicted concentration history and the target concentration for the duration of a simulated 60-min targeted infusion (see text for details). § Different from the recirculatory model, model 3, and model 4 parameters ($P < 0.05$), as determined by Tukey test for multiple comparisons. || Different from model 3 and model 4 parameters ($P < 0.05$), as determined by Tukey test for multiple comparisons. # Different from the recirculatory model and model 4 parameters ($P < 0.05$), as determined by Tukey test for multiple comparisons. ** Different from model 2, model 3, and model 4 parameters ($P < 0.05$), as determined by Tukey test for multiple comparisons. †† Different from model 4 parameters ($P < 0.05$), as determined by Tukey test for multiple comparisons.

NA = not applicable.

Three-compartment Models Fit to Postbolus Data (Models 1 and 2)

Many of the parameters of the three-compartment models fit to postbolus arterial drug concentration data collected either according to a traditional "intense sampling" schedule (model 1) or beginning with the recirculation peak (model 2) differed significantly from those of the recirculatory model (table 1). Of the compartmental volumes, only the V_S s of the three-compartment models did not differ from those of the recirculatory model. The V_C s of the three-compartment models were more than two and one half times the size of that of the recirculatory model, whereas the V_F s were more than 10% larger than that of the recirculatory model; as a result, the volumes of distribution at steady state (V_{SS} s) were approximately 8% larger than that of the recirculatory model. Although the Cl_S s and Cl_E s of these models did not differ significantly from those of the recirculatory model, the Cl_F s of these three-compartment models were nearly 60% and 40% larger than those of the recirculatory model, respectively. Because the Cl_F s of these models exceeded that of the recirculatory model, the sum of all clearances (ΣCl) of the traditional sampling model (model 1) was just 14% less than ΣCl of the recirculatory model (*i.e.*, cardiac output), whereas ΣCl of the recirculation peak model (model 2) was only 22% less than ΣCl of the recirculatory model, despite the fact that neither three-compartment model included the Cl_{ND}

of the recirculatory model, which represents 39% of ΣCl of that model (*i.e.*, 39% of cardiac output).

The effect of the differences in the parameters of the three-compartment models fit to the postbolus data collected according to either a traditional sampling schedule (model 1) or beginning with the recirculation peak (model 2) from those of the recirculatory model are

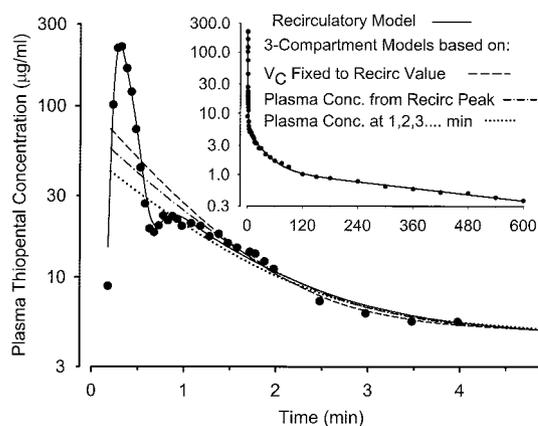


Fig. 3. Arterial blood thiopental concentration histories for the first 5.0 min (illustrating the first- and second-pass peaks) after rapid right atrial injection of 100 mg in a dog anesthetized with 1.5% halothane in oxygen. Arterial blood thiopental concentration histories for 10 h after injection are illustrated in the inset. The symbols represent measured drug concentrations, and the lines represent fits of the recirculatory model and the three-compartment models to the data, which are superimposed on this time scale. V_C = initial distribution volume.

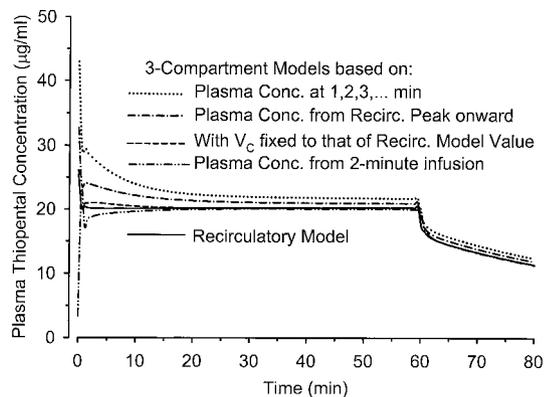


Fig. 4. Drug infusions designed, using the pharmacokinetic parameters of the models indicated in the legend on the figure, to achieve a target thiopental concentration of 20 µg/ml and simulated with the kinetics of the recirculatory model for one dog. V_C = initial distribution volume.

obvious when the target-controlled infusion simulations are considered (fig. 4). The target-controlled drug infusions based on these models exceeded the target concentration from the beginning of the infusion until long after the infusion had begun. The area between the predicted concentration and the target concentration for the infusions based on these models (ΔAUC) greatly exceeded those of any other infusion evaluated in this study (table 1). The increase in the AUCs produced by these infusions represent a more than 13% (model 1) and more than 10% (model 2) increase in the AUC of the infusion over 60 min, much of which occurred within the first 10 min of the infusion. By 10 min, the increase in the AUCs produced by these infusions represent 32% (model 1) and 24% (model 2) increases in the AUC during the infusion.

Three-compartment Model with V_C Fixed to Recirculatory Model Parameters (Model 3)

With V_C fixed to the sum of V_C and V_{ND} from the recirculatory model, the fit of the model to the postbolus data resulted in description of peripheral drug distribution in a manner that was consistent with that of the recirculatory model (table 1). The only parameter of the three-compartment model that differed from that of the recirculatory model was the sum of all clearances (ΣCl), which was less in the three-compartment model because it lacks a nondistributive circuit, hence nondistributive clearance (Cl_{ND}). The consequence of the similarity of the parameters of this three-compartment model to those of the recirculation model was that target-controlled drug infusions based on this model produced a thiopental concentration history predicted by the recirculatory model that differed minimally from the target concentration (fig. 4). The ΔAUC of the resultant concentrations both did not differ from that based on the recirculatory model and was significantly less than those

based on the two other three-compartment models fitted to bolus thiopental concentration data (table 1).

Three-compartment Model Fit to Infusion and Postinfusion Data (Model 4)

The three-compartment model fit to the infusion and postinfusion data (model 4) was similar to that in which V_C was fixed to the sum of V_C and V_{ND} from the recirculatory model (model 3) in that it had a small V_C and described peripheral drug distribution in a manner consistent with its description by the recirculatory model (table 1). Like model 3, the only kinetic parameter of model 4 that differed from those of the recirculatory model was ΣCl . Also like the target-controlled infusions based on model 3, the target-controlled drug infusions based on model 4 produced a thiopental concentration history predicted by the recirculatory model that differed minimally from the target concentration (fig. 4). The ΔAUC of the infusion based on model 4 did not differ from that based on either the recirculatory model or model 3 and was significantly less than those fitted to the other three-compartment models based on bolus thiopental concentration data (models 1 and 2, table 1).

Discussion

Traditional three-compartment mammillary pharmacokinetic models fit to concentration histories obtained after rapid intravenous drug administration (models 1 and 2) do not characterize drug distribution in a manner consistent with its description by the recirculatory model regardless of the sampling schedule used (table 1). This is despite the fact that their fits to the data obtained beginning 5 min after rapid intravenous drug administration are indistinguishable from the fit of the recirculatory model to the same data (fig. 3, inset). Their descriptions overestimate not only V_C but also V_F and Cl_F , as has been reported for propofol in man.²⁶ As a result, target-controlled infusions based on them produce drug concentrations that are significantly above the target concentration until long after the infusion has begun (fig. 4), as is commonly observed with computer-controlled infusions based on traditional mammillary models.⁹

Traditional three-compartment pharmacokinetic models fit to concentration histories obtained after rapid intravenous drug administration are incapable of characterizing drug distribution in a manner consistent with its description by the recirculatory model. Because such models are constrained by the simplifying assumption of instantaneous and complete mixing within V_C , they estimate its volume on the basis of the ratio of the dose to the hypothetical concentration at time zero, determined by back extrapolation of the concentration-versus-time relation (fig. 3). The later one obtains the first blood

sample after rapid intravenous drug administration; the smaller will be the back-extrapolated concentration at time zero and the larger the estimate of V_C . Such an analysis ignores the information available from the first-pass concentration-*versus*-time relation, including the facts that the concentration at time zero is really zero, that there is a temporal lag between the time of intravenous drug administration and the time drug appears at an arterial sampling site, that there may be significant drug uptake by the lung and washout from it, and that mixing even within what might be considered the true V_C is not instantaneous.^{13,14}

Nonetheless, as the current study has demonstrated, it is possible for a traditional three-compartment model to describe drug distribution in a manner consistent with that of the recirculatory model if one circumvents the assumptions underlying the estimation of V_C after rapid intravenous drug administration. In the case of the current study, that was first done by fixing V_C to the sum of V_C and V_{ND} from the recirculatory model (model 3). With a reasonable estimate of V_C , the three-compartment model fit to the data obtained after rapid intravenous drug administration described peripheral drug distribution in a manner that was nearly identical to its description by the recirculatory model (table 1), and the target-controlled drug infusion based on it produced concentrations that deviated minimally from the target (fig. 4).

Given that a three-compartment model is capable of describing drug disposition in a manner consistent with that of a recirculatory model, the question arose as to how to conduct an experiment that would allow one to arrive at such a model without first deriving the recirculatory model. Chiou suggested that better estimates of V_C might be obtained from studies in which the drug of interest is administered by a short-term intravenous infusion because fitting a three-compartment model to data obtained during and after an infusion would avoid many of the erroneous assumptions made when fitting data obtained after rapid intravenous drug administration.^{13,14} Wada and Ward's alfentanil simulations confirmed the wisdom of such an approach.²⁵ Therefore, we generated such data by simulating drug concentrations during a 2-min thiopental infusion and for the subsequent 10 h using the recirculatory pharmacokinetic models. The three-compartment model fit to these data (model 4) had the smallest $V_{C,S}$ of any of the three-compartment models derived in the current study and, like the model based on bolus data in which V_C was fixed to the sum of V_C and V_{ND} of the recirculatory model (model 3), described peripheral drug distribution in a manner that was not different from that of the recirculatory model (table 1). Target-controlled drug infusions based on model 4 deviated minimally from the target (fig. 4). Therefore, this study suggests that the optimal design of a study to obtain pharmacokinetic data

on which to base target-controlled drug infusions would be one in which data are collected during and after a brief drug infusion.

The ability of a target-controlled drug infusion to produce stable drug concentrations at or near the target concentration depends on the pharmacokinetic data set used in designing the infusion.²⁷ Several authors have compared the performance of infusion regimens based on different pharmacokinetic parameter sets. For example, Raemer *et al.*²⁸ compared alfentanil infusions based on population pharmacokinetics derived from data from several studies with those based on pharmacokinetics derived in a smaller study without the benefit of population kinetic analysis. The authors reported that the population kinetics-based infusions had median absolute performance errors that exceeded 50% and were especially inaccurate immediately after the infusion target changed, whereas parameters derived from less sophisticated pharmacokinetic analysis produced infusions having median absolute performance errors less than 20%. The authors could not explain the differences in the performance of the infusions based on these two data sets but noted that the kinetics used to design the better-performing infusion were derived in a study in which alfentanil was administered over several minutes and had a much smaller V_C . The parameters for the poorly performing infusion were derived from a study in which alfentanil was administered by rapid intravenous infusion. Barvais *et al.*²⁹ similarly observed that, of the alfentanil infusions derived from nine different pharmacokinetic data sets, those with the best performance (*i.e.*, median absolute performance errors less than 50%) were those derived from studies in which the drug was administered by slow injection or continuous infusion. Similar observations have been made for fentanyl,³⁰ lidocaine,³¹ and propofol.³²

It might seem from the above that the pharmacokinetics reported for a given drug depend on the mode of drug administration (*e.g.*, bolus *vs.* infusion). An important point of the current study is that the pharmacokinetics of a drug are independent of the mode of administration, but, in the absence of saturation effects, the reported pharmacokinetics depend on the method of study. If the front-end kinetics are estimated with reasonable accuracy (*e.g.*, by a recirculatory model after bolus drug administration or by a three-compartment model during and after drug administration by infusion), they can be used to predict plasma drug concentrations during and after any method of administration.

It was not the purpose of the current study to identify an ideal blood sampling protocol for a study of drug disposition during and after a brief drug infusion. Nonetheless, general recommendations may be made on the basis of the current results. The blood sampling protocol should begin soon after commencing and soon after stopping the drug infusion, but not so soon that samples

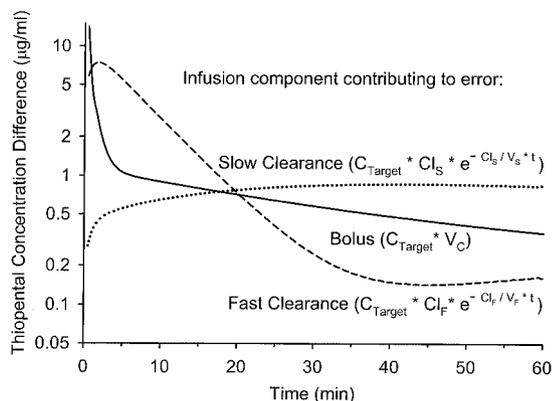


Fig. 5. The relative contributions of the components of the target-controlled drug infusion to the prolonged discrepancy (overshoot) between predicted and targeted concentrations are illustrated. The error resulting from the elimination clearance-matched component was negligible and therefore is not illustrated. The three-compartment model based on the simulated 2-min infusion (model 4) resulted in a nearly perfectly targeted infusion. Therefore, the concentration resulting from each component of the infusion based on model 4 was subtracted from the equivalent component concentration of the infusion based on model 1 for one dog. Equations for each infusion component of the BET dosing regimen²⁴ represented in the figure are included. Cl_F and V_F = rapidly equilibrating tissues; Cl_S and V_S = slowly equilibrating tissues; C_{Target} = target concentration.

are obtained during intravascular mixing transients. Samples should be obtained at regular intervals during the infusion. Postinfusion sampling should be based on sampling theory, which suggests that at least 10 data points are needed to characterize each pharmacokinetic phase (*i.e.*, distribution, redistribution, and elimination), the lengths of which depend on the pharmacokinetic characteristics of the drug and the physiologic system being studied. Thus, for example, the sampling protocol would be expected to be quite different for a muscle relaxant, which has a small volume of distribution, than it is for a hypnotic agent, which has a large volume of distribution. Similarly, the blood sampling protocol would be expected to be different in a patient with an extremely low cardiac output than it is in a patient with a very high cardiac output.

Overestimation of V_C would be expected to result in drug concentrations that are much higher than the target concentrations immediately after commencing a target-controlled drug infusion because the loading dose based on the overestimated V_C would overflow the actual V_C . However, the effect of too large a loading dose on drug concentrations during the infusion would not be expected to be as long lasting as those observed in the current simulations. The sources of the long-lasting discrepancy between the predicted and the targeted concentrations is revealed by comparing the contributions from each component of the infusion based on the 1-, 2-, and 3-min and all subsequent bolus data (model 1) with those from the infusion based on the simulated 2-min infusion data (model 4) (fig. 5). As expected, immedi-

ately after starting the target-controlled infusion, the concentrations exceed the target concentration largely because of the excessive loading dose. However, the loading dose redistributes rapidly. From 1 min to nearly 20 min, the deviation from the target concentration is due largely to the contribution of the target-controlled infusion component based on an overestimation of Cl_F , with significant contribution from the loading dose and a small contribution based on the slight overestimation of Cl_S . Thereafter, the slight deviation from the target concentration was due to the combined effects of the bolus, slow, and, to a lesser extent, fast components of the target-controlled infusion. The only parameter that did not contribute to the deviation from the target concentration was Cl_E , which was the same in all models.

Schnider *et al.*³³ have correctly noted that conventional compartmental models cannot describe drug concentrations after rapid intravenous administration because the monotonic functions of such models cannot describe the recirculatory oscillations observed after bolus drug administration. Therefore, the recirculatory pharmacokinetic model remains the standard for describing the disposition of drugs from the moment of rapid intravenous administration and in identifying the front-end kinetics responsible for interindividual differences in drug response.¹ Nonetheless, the current results suggest that a brief intravenous infusion should be the standardized method of drug delivery from which a three-compartment pharmacokinetic model could be derived that would enable the design of a target-controlled drug infusion that results in concentrations deviating minimally from the target. A three-compartmental model fit to postbolus concentrations without the benefit of information from a recirculatory model could not produce such an accurate infusion.

It is important to emphasize that the infusions in the current study are simulations based on the recirculatory pharmacokinetic model. The underlying assumption of the analysis of the data derived from these simulations is that the concentrations predicted by the recirculatory pharmacokinetic model are a very close approximation of reality. It is possible that the recirculatory pharmacokinetic model is capable of describing drug concentration histories from the moment of rapid intravenous injection accurately but fails to predict concentrations during and after target-controlled or continuous drug infusions. Therefore, the results of the current study should be confirmed in a study in which pharmacokinetic variables derived in the manner proposed are used to design a target-controlled drug infusion that is evaluated rigorously for deviations from the target concentration.

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