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Context-sensitive Half-time in Multicompartment Pharmacokinetic Models for Intravenous Anesthetic Drugs

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Elimination half-life is the pharmacokinetic parameter used most commonly to describe duration of pharmacologic action, including that expected of intravenous anesthetic drugs administered by continuous infusion. Little consideration has been given, however, to the relevance of elimination half-life in describing plasma (central compartment) drug concentrations in the context of relevant infusion durations. Therefore, simulations were performed with multicompartment pharmacokinetic models for six intravenous anesthetic drugs. These models had elimination half-lives ranging from 111 to 577 min. The input in each simulation was an infusion regimen designed to maintain a constant plasma drug concentration for durations ranging from 1 min to 8 h and until steady state. The time required for the plasma drug concentration to decline by 50% after terminating each infusion in each of the models was determined and was designated the "context-sensitive half-time," where "context" refers to infusion duration. The context-sensitive half-times were markedly different from their respective elimination half-lives and ranged from 1 to 306 min. The half-times were explained by posing each pharmacokinetic model in the form of a hydraulic model. These simulations demonstrate that elimination half-life is of no value in characterizing disposition of intravenous anesthetic drugs during dosing periods relevant to anesthesia. We propose that context-sensitive half-times are a useful descriptor of postinfusion central compartment kinetics. (Key words: Anesthetics, intravenous: alfentanil; fentanyl; midazolam, propofol; sufentanil; thiopental. Anesthetic techniques, intravenous: infusion. Computer simulation. Pharmacokinetics.)

THE MOST COMMON RESULT of studies quantifying the pharmacokinetic disposition of drugs administered intravenously are numerical values for parameters describing a linear compartmental model. These model parameters are, or can be used to derive, familiar pharmacokinetic constants such as half-lives, distribution volumes, and intercompartmental rate constants.

When a drug's pharmacokinetic behavior can be described by a one-compartment model (reported frequently but not realistic in theory[1]), it is useful to compute the elimination half-life, the only half-life in a one-compartment model. This half-life can be used to compute the time required for a continuous intravenous infusion to reach a specified fraction of the eventual steady-state central (compare plasma) compartment drug concentration. Likewise, only the elimination half-life is needed to compute the time required for the concentration to decrease by a certain percentage when the infusion is terminated.

In a multicompartment pharmacokinetic model, distribution of drug between the central and peripheral compartments can be a significant contributor to central compartment drug disposition. Although long appreciated for sodium thiopental,[2] the time-varying contribution of distribution processes to the increase and decrease of plasma drug concentrations has remained largely ignored, especially for dose inputs other than a single bolus injection.

Elimination half-life, which provides a parsimonious description of the rate of drug disposition in the one-compartment model, may be of little value in describing multicompartment models, as demonstrated recently by Shafer and Varvel.[3] These authors investigated the complex interaction between pharmacokinetics and pharmacodynamics in predicting the time course of recovery from the potent opioids, and in so doing, highlighted the limited usefulness of the elimination half-life in this regard.

Furthering one aspect of Shafer and Varvel's[3] line of investigation, the purpose of this paper is to simulate the decline in central compartment drug concentration following variable-length infusions in multicompartment pharmacokinetic models for six intravenous drugs used commonly in anesthesia. The time required for the central compartment drug concentration at the end of each infusion to decrease by 50% was defined as a "context-sensitive half-time" and is proposed as a practical allegory of postinfusion central compartment drug disposition.

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Materials and Methods

Multiexponential models describing the pharmacokinetics of alfentanil, fentanyl, midazolam, propofol, sufentanil, and thiopental were compiled from the published literature. These models were unit disposition functions[4] of the form $udf(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} + A_3e^{-\lambda_3 t}$ where udf(t) is the central compartment drug concentration

TABLE 1. Pharmacokinetic Model Parameters Used in Simulations

Model	A_1 (l^{-1} or kg/l*)	λ_1 (min^{-1})	A_2 (l^{-1} or kg/l*)	λ_2 (min^{-1})	A_3 (l^{-1} or kg/l*)	λ_3 (min^{-1})	Elimination Half-life (min)
Alfentanil	3.772×10^{-1}	1.03×10^{0}	5.454×10^{-2}	5.20×10^{-2}	2.272×10^{-2}	6.20×10^{-3}	111
Fentanyl	6.923×10^{-2}	6.70×10^{-1}	6.153×10^{-3}	3.70×10^{-2}	1.538×10^{-3}	1.50×10^{-3}	462
Midazolam	—	—	$*1.896 \times 10^{0}$	4.15×10^{-2}	$*3.640 \times 10^{-1}$	3.99×10^{-3}	173
Propofol	4.420×10^{-2}	2.56×10^{-1}	5.658×10^{-3}	2.93×10^{-2}	9.038×10^{-4}	2.46×10^{-3}	280
Sufentanil	4.666×10^{-2}	4.80×10^{-1}	8.333×10^{-3}	3.00×10^{-2}	5.555×10^{-4}	1.20×10^{-3}	577
Thiopental	$*2.148 \times 10^{0}$	2.74×10^{-1}	$*1.120 \times 10^{0}$	1.50×10^{-2}	$*4.314 \times 10^{-1}$	2.00×10^{-3}	346

These parameters are for unit disposition functions of the form $udf(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t}$, where t is time in minutes.

Elimination half-life = $(\ln 2)/\lambda_3$.

profile resulting from a unit (1 mg, 1 μg, *etc.*, as appropriate) bolus (impulse) input, and $\lambda_1 > \lambda_2 > \lambda_3$. Elimination half-life was calculated as $(\ln 2)/\lambda_3$. The model parameters and corresponding elimination half-life values used in this study are listed in table 1. The coefficients and rate constants listed in the table for the two- or three-exponential unit disposition models were used to calculate[5] rate constants and volumes for the corresponding two- or three-compartment model (table 2).

Equation 1 in the Appendix was used to simulate the central compartment drug concentration *following termination* of BET-type infusions lasting 1–500 min. By "BET-type infusion" we refer to the well-known dosing regimen computed (based on the parameters of the two- or three-compartment model being simulated) to instantaneously achieve and maintain a constant central compartment drug concentration.[6] Equation 2 in the Appendix was used to simulate the central compartment drug concentration following termination of an infinitely long infusion (*i.e.*, after all compartments have come into equilibrium with the central compartment). For the sake of simplicity, the dosing regimen used with each of these linear pharmacokinetic models was designed to maintain a central compartment drug concentration of 100 ng/ml (Cp_d in equation 1) throughout the infusion. We were able to select this arbitrary level because of the linearity of the models and because we were interested only in relative (percentage) changes in concentration. All simulations were performed using a software program written by us.

The central compartment drug concentrations following each infusion were recorded at 5-s intervals. The time (minutes) required for the simulated central compartment drug concentration to decrease from its value (100 ng/ml) at the end of the infusion to 50 ng/ml (a 50% decrease) was determined for each simulation performed. We will refer to this result (the time required for a 50% decrease in the central compartment drug concentration) as a "context-sensitive half-time," in which "context" is the duration of the infusion.

The model parameters used for alfentanil,[7] fentanyl,[7] and sufentanil[8] were selected based on the recommendations in reference 3. The model parameters used for midazolam[9] and propofol[10,11] were based on those demonstrating reasonable predictive accuracy in pharmacokinetic model-driven infusion devices. The parameters used for thiopental[12] have likewise provided reasonable predictive accuracy in our own limited experience (unpublished data) using thiopental in clinical studies with our own pharmacokinetic model-driven infusion device.[13]

Results

Shown in figure 1 are context-sensitive half-times as a function of infusion duration for each of the models simulated. For ease of comparison, the context-sensitive half-times computed following termination of 1-min, 1-h, 3-h, and 8-h infusions and after infusion to steady-state are given in figure 2 relative to the corresponding elimination half-life value for each of the models analyzed.

TABLE 2. Compartment Volumes and Intercompartmental Clearances (Derived from the Model Parameters in Table 1)

Model	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{13} (min^{-1})	k_{31} (min^{-1})	V_1 (l)	V_2 (l)	V_3 (l)
Alfentanil	8.946×10^{-2}	6.540×10^{-1}	2.089×10^{-1}	1.179×10^{-1}	1.775×10^{-2}	2.2	6.9	14.6
Fentanyl	5.940×10^{-2}	3.725×10^{-1}	9.597×10^{-2}	1.740×10^{-1}	6.522×10^{-3}	13	50.4	347
Midazolam	1.651×10^{-2}	—	—	1.895×10^{-2}	1.003×10^{-2}	30.9	—	58.5
Propofol	6.923×10^{-2}	1.006×10^{-1}	5.685×10^{-2}	5.634×10^{-2}	4.687×10^{-3}	19.7	34.8	236
Sufentanil	6.629×10^{-2}	2.701×10^{-1}	1.009×10^{-1}	7.127×10^{-2}	2.583×10^{-3}	18	48.2	497
Thiopental	1.240×10^{-2}	1.374×10^{-1}	1.216×10^{-1}	1.396×10^{-2}	5.445×10^{-3}	18.9	21.3	48.5

V_i = volume of i-th compartment. By convention and definition, compartments 2 and 3, respectively, were taken to be the fast and slow compartments. Midazolam and thiopental values are for a 70-kg subject.

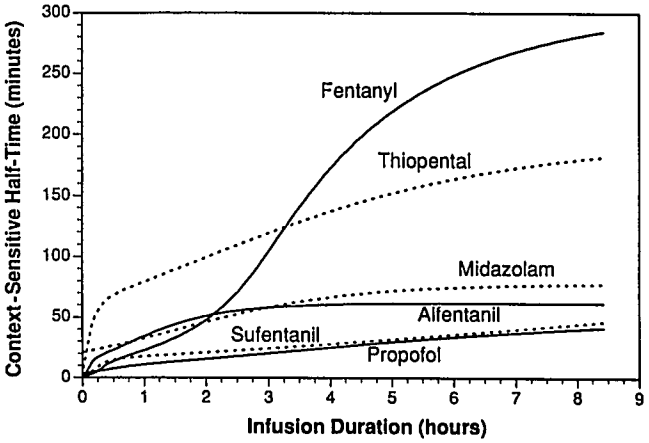

FIG. 1. Context-sensitive half-times as a function of infusion duration for each of the pharmacokinetic models simulated. Solid and dashed line patterns are used only to permit overlapping lines to be distinguished.

Discussion

Relevance of Elimination Half-Life

Elimination half-life, defined as $(\ln 2)/\lambda_3$, is the descriptor used most often by clinicians and pharmacologists to characterize a drug's pharmacokinetic behavior. In a strictly mathematical construct, however, half-life is useful in the computation of central compartment drug concentrations only in the one-compartment model. Some of the limitations of elimination half-life as a concept[14] and with specific regard to multicompartment models[3] have been discussed in previous works, but the perpetual popularity of half-life attests to its perceived utility.

We performed simulations using pharmacokinetic models with elimination half-lives ranging from 111 min (alfentanil model) to 577 min (sufentanil model). These models described the pharmacokinetics of six drugs in common clinical use. Following infusions designed to maintain a constant central compartment drug concentration for periods ranging from 1 min (compare bolus) to 8 h, the time for the simulated central compartment drug concentration to decrease from its value at the end of the infusion to 50% of this value ranged from 1 min to 280 min (figs. 1 and 2). These data demonstrate that in the context of dosing schemes and durations relevant to the manner in which the drugs represented by these multicompartment models are used, the classical elimination half-life is of no apparent value in predicting the decline of central compartment drug concentrations for the six models analyzed.

Specifically, these simulations demonstrate the sustained influence of distribution processes[15] in governing drug disposition. By distribution processes we refer to both the net transfer of drug out of the plasma and into the peripheral compartments and the reverse process whereby there is a net transfer of drug back to the central compartment.

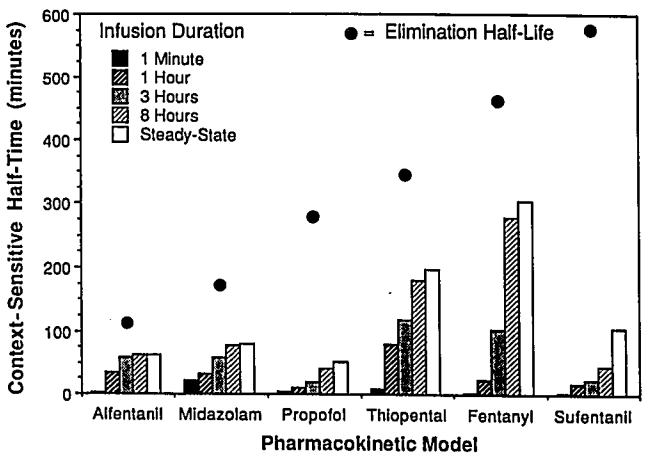

FIG. 2. Context-sensitive half-times (bars) redrawn from figure 1 for each of the pharmacokinetic models after terminating a 1-min, 1-h, 3-h, 8-h, or infinitely long (*i.e.*, to steady state) BET-type infusion shown relative to the elimination half-life (dots) computed from each model.

Semiquantitative Explanation of Context-Sensitive Half-Times

The three-bucket hydraulic model shown in figure 3 is a physical analog of the three-compartment mathematical model. More to the point, the differential equations describing the height of the water level in each bucket are of the same form as those describing the drug concentration in each compartment of the three-compart-

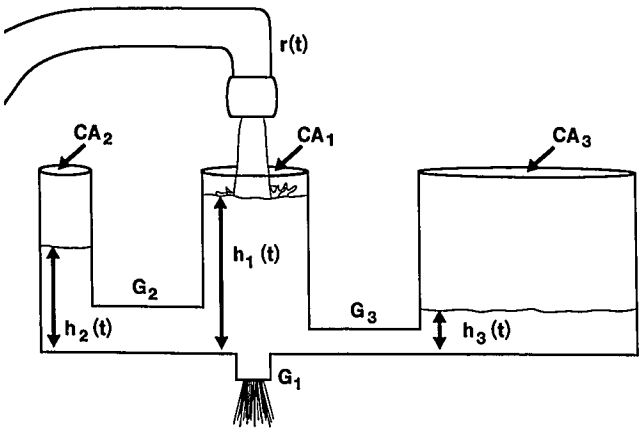

FIG. 3. Hydraulic model analogy to three-compartment pharmacokinetic model. The height, $h_i(t)$, of the water level in the i-th bucket is analogous to the drug concentration in the i-th compartment. Each bucket is characterized by a cylindrical area, CA_i, and the pipes connecting the buckets with each other or the outside world are characterized by a conductance, G_i. Water enters bucket 1 at the rate r(t) and leaks irreversibly through G_1.

ment model. Using the hydraulic model, we can provide an intuitive rationale for the role of distribution in determining postinfusion central compartment kinetics.

The model in figure 3 consists of a central bucket, bucket 1, connected by pipes to two peripheral buckets, buckets 2 and 3, which are not connected to each other. The volume of water in each bucket is analogous to the amount of drug in each compartment of the corresponding compartment model. Likewise, the *height* of the water level in each bucket is analogous to the *concentration* of drug in each compartment of the corresponding compartment model.

The rate, r(t), at which water pours into bucket 1 is analogous to the intravenous drug infusion rate. The rate, $G_i(h_1(t) - h_i(t))$, at which water flows between bucket 1 and bucket i is proportional to the difference in the height, $h_1(t)$ and $h_i(t)$, of the water levels in buckets 1 and i, respectively, where i = 2 or 3 and G_i is the conductance (reciprocal of resistance) of the tube connecting buckets 1 and i. A positive value for $G_i(h_1(t) - h_i(t))$ implies flow out of bucket 1 into bucket i, and a negative value for this quantity indicates flow in the opposite direction (*i.e.*, water flows down pressure gradients). Water leaks out of bucket 1 at a rate $G_1h_1(t)$, where G_1 is the conductance of the hole in bucket 1.

In keeping with the methodology used in the foregoing, consider r(t) to be contrived so that $h_1(t)$ is maintained constant at the value H_1. If r(t) continues indefinitely, it is clear from inspection of figure 3 that $h_2(t)$ and $h_3(t)$ will also eventually be equal to H_1, at which point G_1H_1 will equal r(t). This is analogous to assuming the concentration of drug in each compartment of a multicompartment model to be equal at steady state during a very long infusion into the central compartment.[16]

The hydraulic model is defined by the conductances, G, of the three pipes and the cylindrical area, CA, of each of the three buckets. The relationship between the parameters of the water model and the parameters of the three-compartment model are listed in table 3. We believe the functions listed in table 4, which are derived from the hydraulic model parameters, can be used to provide an intuitively appealing explanation for context-sensitive postinfusion kinetics, as demonstrated in the remainder of this section.

TABLE 3. Relationship Between Parameters of Three-bucket Hydraulic Model and Parameters of Three-compartment Mathematical Model

Hydraulic Model		Compartment Model
Conductances		
G_1	=	$\hat{V}_1k_{10}$
G_2	=	$\hat{V}_1k_{12}$
G_3	=	$\hat{V}_1k_{13}$
Cylindrical areas		
CA_1	=	$\hat{V}_1$
CA_2	=	$k_{12}\hat{V}_1/k_{21}$
CA_3	=	$k_{13}\hat{V}_1/k_{31}$

$\hat{V}_1$ = V_1 normalized to appropriate units by dividing by 1 mm (*i.e.*, ml/mm = $mm^3/mm = mm^2$).

TABLE 4. Computation of Time Constants and Conductance Ratios for Three-bucket Hydraulic Model and Three-compartment Mathematical Model

Hydraulic Model		Compartment Model
Equlibration time constants		
$TC_2 = CA_2/G_2$	=	k_{21}^{-1}
$TC_3 = CA_3/G_3$	=	k_{31}^{-1}
Elimination time constant		
$TC_1 = CA_1/G_1$	=	k_{10}^{-1}
Conductance ratios		
G_2/G_1	=	k_{12}/k_{10}
G_3/G_1	=	k_{13}/k_{10}

While $h_1(t)$ is held constant at H_1, $h_2(t)$ and $h_3(t)$ approach H_1 at rates dependent only on G_2 and CA_2 and on G_3 and CA_3, respectively. In particular, time-constants, TC_2 and TC_3, can be defined (table 4) as CA_2/G_2 and CA_3/G_3, respectively, which have units of time. Considering buckets 2 and 3 to be initially empty and $h_1(t) = H_1$, the time-constants can be interpreted in a manner that is qualitatively similar to half-life. For example, after TC_2 minutes, the water level in bucket 2 will have risen to 63% of H_1; after $2TC_2$, to 86% of H_1; after $3TC_2$, to 95% of H_1; and so forth. The larger the time-constant of the pipe-peripheral bucket combination, the longer it takes for the water level in that bucket to equilibrate with the level in bucket 1.

When the infusion maintaining the water level in bucket 1 at H_1 is terminated, the rate at which the water level in bucket 1 will decrease is dependent on both elimination and distribution phenomena. Elimination is the intrinsic ability of bucket 1 to empty itself irreversibly, the rate of which is a function of the cylindrical surface area of the bucket and the conductance of the hole in the bucket. Accordingly, we can define (table 4) an elimination time-constant, $TC_1 = CA_1/G_1$. With r(t) = 0 and in the absence of additional flow of water into, or return of water from, the peripheral buckets, the water level in bucket 1 TC_1 minutes after terminating the infusion would be 37% of H_1; after $2TC_1$ would be 14% of H_1; and so forth. The smaller TC_1, the faster $h_1(t)$ decreases.

Postinfusion kinetics in a multibucket model are more complicated than this, though. In particular, water will continue to flow into peripheral bucket i as long as $h_1(t)$ is greater than $h_i(t)$. Continued flow of water into a peripheral bucket, acting in combination with elimination, can produce an initially rapid postinfusion decrease in $h_1(t)$. The water level in each of the peripheral buckets will equilibrate with $h_1(t)$ at a different time, but once $h_1(t)$ falls below $h_i(t)$, water in bucket i will begin flowing back to bucket 1, again at a rate determined by $G_i(h_1(t)$

$- h_i(t))$ for i = 2 or 3. The return of water from the peripheral buckets acts in opposition to the effort of G_1 to lower the water level in bucket 1. We propose (table 4) that the ratio of conductances, G_i/G_1, is a useful indicator of the postequilibration influence of bucket i on the postinfusion kinetics observed in bucket 1.

Although this ratio is a gross simplification of the complex interrelationships between the buckets and pipes, a large value for G_i/G_1 does suggest that bucket i returns water to bucket 1 at a rate fast enough to minimize the gradient between $h_i(t)$ and $h_1(t)$. Likewise, a small value for G_i/G_1 suggests that water trickles back from bucket i so slowly relative to the removal of water through G_1 that a large gradient between $h_i(t)$ and $h_1(t)$ will result during the postinfusion period. Clearly, the larger the conductance ratio, the more $h_1(t)$ is bolstered by water returning from the peripheral bucket, and thus the more slowly $h_1(t)$ declines. The conductance ratio that we have calculated does not account for the *amount* of water that is returning from the peripheral bucket, but this is incorporated as necessary in the analysis that follows.

Using the compartmental parameter values in table 2 and the algebraic relationships in tables 3 and 4, we computed numerical values for the time constants for peripheral equilibration, the elimination time constant, and conductance ratios for the six pharmacokinetic models included in this study. The results are presented graphically in figures 4 and 5. A thorough discussion of the implications of these figures is beyond the scope of this paper, but we do wish to highlight several observations that help to explain the context-sensitive half-times given in figure 2. In doing so, we will return to familiar pharmacokinetic nomenclature (*i.e.*, central compartment, peripheral compartments, plasma drug concentration, *etc.*) with the understanding that we could just as well speak in terms of buckets and water levels. (We wish to point

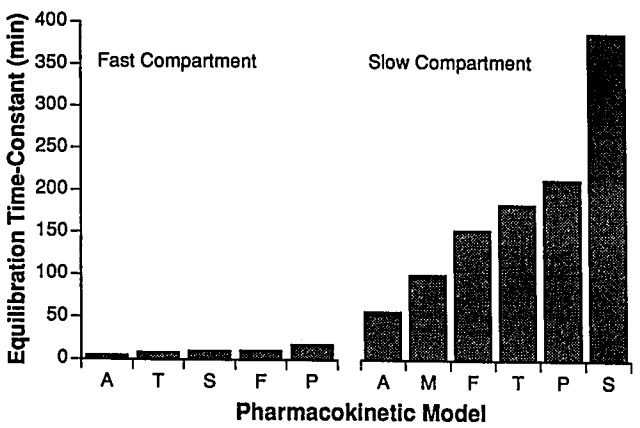

FIG. 4. Equilibrium time constants for the fast and slow compartments for each pharmacokinetic model. A = alfentanil; F = fentanyl; M = midazolam; P = propofol; S = sufentanil; T = thiopental.

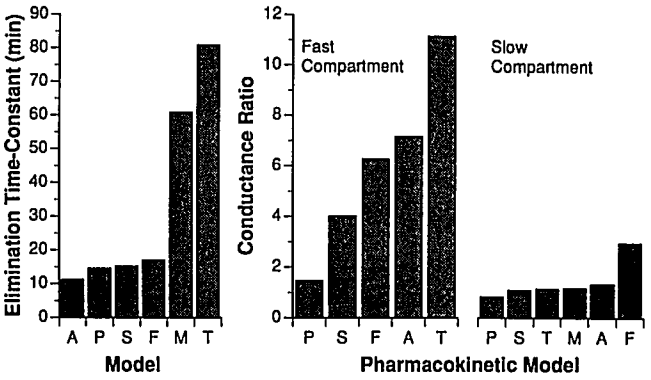

FIG. 5. Elimination time constant and conductance ratios for each pharmacokinetic model. A = alfentanil; F = fentanyl; M = midazolam; P = propofol; S = sufentanil; T = thiopental.

out only as an aside that calculation of G_i/G_1 is conceptually and numerically equivalent to calculating $\text{clearance}_i/\text{clearance}_1$, where clearance_i is an intercompartmental clearance, $V_1k_{1i} = V_ik_{i1}$, and clearance_1 is central clearance, V_1k_{10}.)

The most straightforward way to explain the context-sensitive half-times is to begin with a semiquantitative rationalization of the steady-state half-times. On the basis of elimination time constant alone, we would, for example, expect fentanyl to have a steady-state half-time that is little different from that for the propofol model. On inspection of figure 2, however, we observe that the steady-state half-time for the fentanyl model is almost an order of magnitude larger than that for propofol. Stated another way, the steady-state half-time for the fentanyl model is about twenty times the value that would be predicted from the elimination time constant, whereas the steady-state half-time for propofol is only about four times larger than expected.

Fentanyl's long steady-state half-time is a result of the large conductance ratio (fig. 5) associated with the slow compartment in this model. (The conductance ratio for fentanyl's slow compartment is larger than the conductance ratio for propofol's fast compartment!) The volumes of the three compartments in the fentanyl and propofol models are reasonably comparable, and in particular the third (slow) compartment in both models is huge. The large conductance ratio for the slow compartment in the fentanyl model suggests that the postinfusion postequilibration fentanyl concentration gradient between the third and central compartments will be smaller in the fentanyl model than in the propofol model. Because the third compartment in the fentanyl model is so big, a large quantity of drug will have to return to the central compartment per unit time to keep the concentration gradient at a minimum. Stated another way, much of the drug that is eliminated from the plasma by the processes giving the

fentanyl model a reasonably brief elimination time constant is replaced immediately by fentanyl flooding back from the slow compartment. In contrast, net release of drug from both peripheral compartments in the propofol model is sluggish enough that elimination processes can lower the central compartment with little hindrance.

As another example, consider that, as in the propofol model, the steady-state half-time for the thiopental model is only a few times larger than would be expected on the basis of the elimination time constant alone. This occurs despite a huge fast-compartment conductance ratio. Note, however, that the volume of the fast compartment in the thiopental model (table 2) is small relative to its central compartment volume. This means that the quantity of thiopental that must return to the plasma per unit time to keep the drug concentration in the second compartment at near equilibrium with the declining central compartment drug concentration is insufficient to impede the central elimination process substantially. In addition, the slow compartment conductance ratio for the thiopental model is small enough that the return of drug from this compartment has only a modest effect on the central compartment drug concentration.

With the foregoing discussion we are proposing that steady-state half-times can be understood by considering, first, the elimination time constant and, second, the ability of the peripheral compartments to preserve the central compartment drug concentration during the postinfusion period. The only mechanism that can produce a half-time less than the steady-state maximum is postinfusion distribution into nonequilibrated peripheral compartments.

For the pharmacokinetic models considered in this paper, it is unlikely that both peripheral compartments will be in equilibrium with the plasma drug concentration at the time of terminating an infusion of typical intraoperative duration. As the names suggest, the fast compartments in these pharmacokinetic models equilibrate (*i.e.*, reach greater than 95% of their steady-state concentration) with their central compartment rather quickly (*i.e.*, 30–60 min) after the start of an infusion, based on the equilibration time constants given in figure 4. The slow compartments, on the other hand, require (fig. 4) that the infusion continue for many hours (almost a day for the sufentanil model!) before near equilibration is achieved.

At the termination of a bolus or very brief infusion, neither peripheral compartment will have had time to equilibrate with the plasma and, therefore, continued net distribution into both compartments, acting in addition to elimination processes, decreases the central compartment drug concentration rapidly. The combined influence of these effects is demonstrated by the very short 1-min context-sensitive half-times recorded in figure 2. The relatively long 1-min half-time for midazolam results from the absence of a fast compartment in the pharmacokinetic model used for this drug.

At the termination of longer infusions, the fast compartment in each of these models will be essentially equilibrated with the plasma and will be unable to accept additional drug from the central compartment to hasten the postinfusion decrease in the plasma drug concentration. The slow compartment, however, will not, in general, have had time to equilibrate with the plasma, and the concentration gradient between the central and slow compartments will cause drug to continue flowing into the slow compartment. Eventually, the declining plasma drug concentration and the rising slow compartment drug concentration equilibrate; thereafter, continuing decline of the central compartment drug concentration occurs by the mechanisms governing the steady-state half-time.

In general, the shorter the equilibration time constant for the slow compartment, the shorter is the infusion duration required for the postinfusion kinetics to resemble those that result from an infinitely long infusion. For example, notice that both equilibration time constants (fig. 4) for the alfentanil model are relatively brief. Consistent with this, the 8-h half-time calculated for alfentanil (fig. 2) is virtually equal to alfentanil's steady-state half-time. In contrast, the 8-h half-time calculated for the sufentanil model, which has the longest slow compartment equilibration time constant among the six models, is but a modest percentage of the steady-state half-time.

The notion of half-time is no more intrinsic to a multicompartment model than those of, for example, a 20%-time or a 90%-time. It was somewhat of a contrivance, therefore, to use time constants and "conductance ratios" to rationalize the half-times that were calculated in this study. Nevertheless, posing each of the pharmacokinetic models in the form of a hydraulic model led us to analyze postinfusion kinetics in a manner that was much more intuitive than we had attempted previously.

Hydraulic models have been used extensively to describe pharmacokinetics of the inhalation anesthetic drugs[17] but have not been popular in the literature describing intravenous drugs. A notable exception, 25 yr ago Saidman and Eger[18] used both a hydraulic model and an electric circuit model to discuss the pharmacokinetics of thiopental. Pharmacokineticists have been slow to adopt hydraulic models, but we now believe that these and other physical analogs do offer conceptual advantages when one is attempting to understand the implications of intercompartmental rate constants, hybrid rate constants, and compartmental volumes.

Consideration of the Study Design

Interpretation of the data presented in this paper must be predicated on four important considerations. First, the

pharmacokinetic parameter sets used in these simulations were selected, to the extent that data were available, on the basis of documented prospective accuracy in predicting plasma drug concentrations during infusions. It is acknowledged, however, that the pharmacokinetic model used for each drug did not reflect inter- or intrasubject variability and that there are vast discrepancies between the various models and parameter sets that have been proposed in the literature for the drugs included here. This qualification notwithstanding, this study demonstrates unequivocally that pharmacokinetic models with relatively long elimination half-lives can predict relatively brief context-sensitive half-lives. The reader will appreciate that the purpose of this paper was not to critique the applicability of multiexponential pharmacokinetic models or the accuracy of their parameters.

Second, we have investigated only pharmacokinetic disposition and have not attempted to incorporate pharmacodynamic factors. The times required for effect-site, rather than plasma, drug concentrations to decrease by 50% would be expected to be somewhat longer than those indicated in figure 1. Readers interested in pursuing this issue in greater detail are referred to the paper by Shafer and Varvel,[3] which is an excellent treatise on the combined influence of pharmacokinetic and pharmacodynamic factors on recovery times for the opioid analgesics.

Third, it is important to appreciate that, as the name implies, we have defined context-sensitive half-time in terms of the time required for a 50% decline in the central compartment drug concentration. Context-sensitive half-time is not a half-life and cannot be used as such. A decrease of 50% was used in defining context-sensitive half-time because of the well-entrenched notion of *half*-life in pharmacokinetics. This definition may give context-sensitive half-time practical significance as a time-to-recovery index when the central compartment drug concentration maintained intraoperatively has been about twice that required for adequate recovery from the drug's effect. Currently, there are insufficient clinical data to know whether 50% or some other percentage would provide the most clinically useful description of plasma drug disposition following practical infusion regimens. It is clear, however, that some sort of context-sensitive index will be more applicable than elimination half-life.

Finally, BET-type infusion regimens were used in all of our simulations. The BET approach analytically mimics clinical practices where a variable-length continuous infusion is preceded by a loading dose to achieve a relatively stable central compartment drug concentration. By using a BET input to the pharmacokinetic models, "context-sensitive" half-lives were obtained in the context of central compartment drug concentrations after having been maintained by a clinically relevant dosing scheme for clinically relevant periods of time.

The simulations presented here and those of others[3] suggest that it is critically important to discuss and quantify pharmacokinetic descriptors with respect to specific, practical contexts. We propose context-sensitive half-time as a useful pharmacokinetic descriptor and look forward to clinical validation of its accuracy and applicability. These issues are of particular importance to the practice of anesthesiology, in which the implications of pharmacokinetic misinterpretation are realized in minutes rather than in hours or days.

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Appendix

The infusion regimen required to maintain a constant central compartment drug concentration of Cp_d in an n-compartment model consists of a bolus of size $V_1 \times Cp_d$ followed immediately with a constant-rate continuous infusion at a rate of $V_1 \times Cp_d \times k_{10}$ superimposed on $n - 1$ exponentially declining infusions of $\sum_{i=2}^{n} V_1 Cp_d k_{1i} e^{-k_{1i}t}$. This is the well-known BET dosing regimen.

It can be shown that convolution of this input with the n-exponential unit disposition function of the form $\sum_{i=1}^{n} A_i e^{-\lambda_i t}$ (from which the constants defining the compartment model are derived) yields the following equation, giving the central compartment drug concentration c(t′) at any time t′ following termination of the infusion regimen:

$$c(t') = V_1 Cp_d \left\{ \sum_{i=1}^{n} A_i e^{-\lambda_i t'} \left[e^{-\lambda_i T} + \frac{k_{10}}{\lambda_i} (1 - e^{-\lambda_i T}) + \sum_{j=2}^{n} \frac{k_{1j}}{k_{j1} - \lambda_i} (e^{-\lambda_i T} - e^{-k_{j1} T}) \right] \right\} \quad (1)$$

where T is the duration of the infusion. To clarify, if a 1-h infusion began at time zero, and we are interested in the central compartment drug concentration 10 min after terminating the 1-h infusion, we would calculate c(10 min) with T = 60 min.

As T approaches infinity (*i.e.*, the time required for all compartments to reach equilibrium during a continuous infusion), equation 1 reduces to the following form, which gives the central compartment drug concentration at any time t′ following termination of an infusion to steady-state:

$$c(t') = V_1 k_{10} Cp_d \left\{ \sum_{i=1}^{n} \frac{A_i}{\lambda_i} e^{-\lambda_i t'} \right\} \quad (2)$$

Note that equation 2 is of the same multiexponential form as the unit disposition function; only the magnitude of the weighting on each of the exponential terms is changed. Thus, the decrease in central compartment drug concentration will be multiexponential even following an infinitely long infusion.