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EDITORIAL VIEWS

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Improving the Clinical Utility of Anesthetic Drug Pharmacokinetics

Pharmacokinetic characterization of intravenous drugs usually consist of two steps. In the first step, the pharmacokinetic parameters are described by fitting a model to the observed data. Frequently, the model consists of a multicompartment mammillary model that yields one or two distribution half-lives and a terminal "elimination" half-life. In the second step, the pharmacokinetics are placed in clinical perspective. This is often done by contrasting the half-lives from the study with the half-lives of either the same drug in a different population or of a different drug in the same population. The investigators then conclude with something like: "The prolonged half-life in patients with hepatic failure suggests that [drug x] should be avoided in this population, particularly because no such change is observed with [drug y]."

In this issue of ANESTHESIOLOGY, Hughes *et al.*[1] demonstrate that conventional interpretation of half-lives, as described above, is simplistic and, to be blunt, wrong. Hughes *et al.* do not take issue with the reported half-lives for several commonly used intravenous drugs (alfentanil, midazolam, propofol, thiopental, fentanyl, and sufentanil). Building on the work of Shafer and Varvel,[2] Hughes *et al.* convincingly demonstrate that the half-lives, in and of themselves, provide virtually no insight about the rate of decline in concentration following drug administration.

The purpose of this editorial is to examine the concepts presented by Hughes *et al.* and to direct the reader's attention to the pharmacokinetic concepts that are clinically relevant to anesthetic practice. We also hope to provide readers with the ability to identify unsupported pharmacokinetic conclusions in the literature. We will use a fictitious new drug, Duzitol (probably a combination hypnotic, analgesic, amnestic, and muscle relaxant), to illustrate the extent to which conventional pharmacokinetic analysis can produce misleading conclusions.

Let us assume that investigators have conducted a comparison of Duzitol in two populations: a control population of healthy surgical patients and a population with severe hepatic failure. Table 1 shows the pharmacokinetic parameters from this study: the α and β distribution half-lives, the terminal γ half-life, the clearance, the central volume, and the volume of distribution at steady state (Vd_{ss}). These are the parameters frequently reported in such studies, and all of the parameters for a three-compartment model can be calculated from these six parameters. The investigators also reference propofol pharmacokinetics[3] for a 50-yr-old, 70-kg man, for purposes of comparison.

The fictitious investigators then draw the following conclusions from table 1:

1. The decrease in plasma concentrations following Duzitol infusions in normal subjects will be extremely rapid because of the very short half-lives.
2. Duzitol should be avoided in patients with hepatic failure, because the half-lives in hepatic failure are *four times longer* than in normal subjects and clearance is decreased by 25% in this population.
3. The volume of the central compartment for Duzitol

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Address reprint requests to Dr. Shafer: Anesthesiology Service (112A), Palo Alto Veterans Administration Medical Center, 3801 Miranda Avenue, Palo Alto, California 94304.
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TABLE 1. Comparative Pharmacokinetics of Duzitol

	Duzitol		
	Normal Subjects	Hepatic Failure	Propofol: Normal Subjects
Half-lives (min)			
Rapid distribution	1.0	4.0	0.8
Slow distribution	10.0	40.0	7.8
Terminal elimination	100	400	198
Metabolic clearance (l/min)	0.68	0.51	1.9
Central volume (l)	7.6	5.0	6.3
Vd_{ss} (l)	66	93	284

Vd_{ss} = volume of distribution at steady state.

is reduced by 34% in hepatic failure, probably as a result of decreased cardiac output and concomitant diuretic therapy in this population.

4. The Vd_{ss} is markedly increased in hepatic failure, most likely as a result of anasarca and uptake of Duzitol by ascitic fluid. With such a high Vd_{ss}, the authors again caution against the use of Duzitol in patients with hepatic failure, particularly in long cases, because there will be substantial accumulation of drug leading to slow recovery.
5. The authors point out that the distribution half-lives of Duzitol are quite similar to propofol, whereas the terminal half-life of Duzitol is substantially more rapid than that of propofol. In addition, they note that the Vd_{ss} is far smaller for Duzitol. These observations lead them to suggest that patients receiving Duzitol will have faster emergence than those receiving propofol, particularly after long infusions to steady state.

In summary, the authors conclude that Duzitol is a promising new drug with rapid distribution and elimination half-lives that should result in more rapid recovery than that following propofol administration, but that the drug should not be used in patients with hepatic failure because of the probability of exceeding slow recovery. These are, *a priori*, totally reasonable and sound conclusions. *They are also dead wrong.* The pharmacokinetics of Duzitol shown in table 1 actually predict exactly the opposite conclusions.

Let us assume, as Hughes *et al.* have assumed in their article, that we give Duzitol in a manner that maintains a constant plasma drug concentration. Strictly speaking, this requires a computer-controlled infusion. However, the assumption is a reasonable approximation of the standard clinical setting (if we may generalize from our own experience) because clinicians attempt to find some combination of boluses and infusions to achieve a reasonably steady plasma drug concentration that produces a constant level of drug effect.

Figure 1 shows the time required for a 50% decrease in plasma concentration following termination of a continuous infusion, based on a computer simulation using the parameters in table 1. In contrast to the predictions arrived at from a simplistic analysis of the pharmacokinetic parameters in table 1, the computer simulation shows that:

1. In normal patients, recovery (defined as a 50% decrease in plasma drug concentration) from a Duzitol infusion will be *slower* than recovery from a propofol infusion.
2. In patients with hepatic failure, recovery from a Duzitol infusion will be much *faster* than recovery in the absence of hepatic failure.
3. Duzitol is an excellent choice for patients with hepatic failure undergoing long procedures.
4. After termination of infusions that have reached steady state, plasma concentrations will decline by 50% in 41, 10, and 20 minutes for Duzitol in normal subjects, Duzitol in subjects with hepatic failure, and propofol in normal subjects, respectively.

How do we reconcile the seemingly reasonable conclusions of our hypothetical investigators with the actual predictions of the pharmacokinetics? First, for drugs described by multicompartment pharmacokinetics, half-lives do not predict the rate of recovery following drug administration. The terminal half-life only sets an upper bound on how much time will be required for a 50% decrease in plasma concentration. The rate of recovery is invariably faster than the terminal elimination half-life, even after infusions

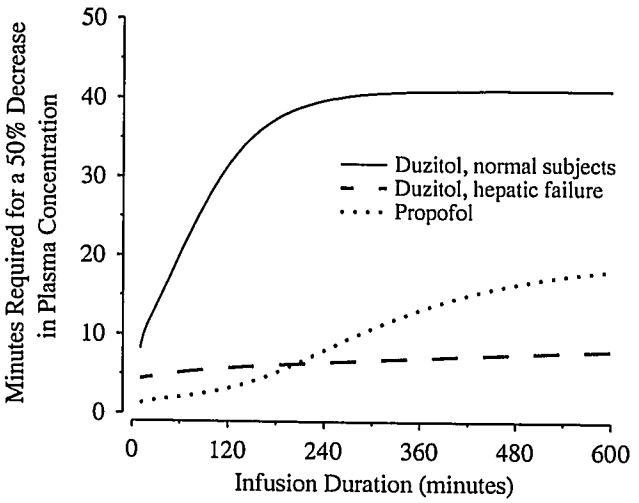

FIG. 1. Curves showing the time required for a 50% decrease in Duzitol concentrations following termination of a steady-state infusion in normal patients (solid line), Duzitol concentrations in patients with hepatic failure (dashed line), and propofol in a 50-yr-old, 70-kg man (dotted line), as a function of the duration of the infusion.

to steady state. This is particularly marked when Duzitol is administered to patients with hepatic failure. In these patients, the terminal half-life is 400 min, yet the Duzitol concentrations fall by 50% in only 10 min after infusions to steady state.

When describing drugs with multicompartment pharmacokinetics, investigators estimate the slopes and intercepts of several log-linear lines that, when superimposed, define the plasma decay curve following bolus injection. The slopes of these lines are inversely proportional to the half-lives, whereas the intercepts or coefficients represent the amount that each half-life contributes to the decrease in concentration following a bolus dose. These coefficients can be expressed as a percent of the sum of all coefficients, as shown in table 2. Figure 2 compares the percent decline in Duzitol concentration following a bolus dose in normal patients and in patients with hepatic failure. The inset in figure 2 shows that the more rapid initial half-life in normal individuals lowers the concentrations by approximately 75%, as suggested by table 2, whereas in patients with hepatic failure the initial half-life, albeit slower, is responsible for a 97.5% decrease. By 30 min the concentrations in patients with hepatic failure are only one third of the concentrations in normal patients, despite the more rapid initial half-life in normal patients.

The same applies to the terminal elimination half-life. The larger graph in figure 2 shows that the terminal elimination half-life is responsible for the last 5% decline in normal patients but only 0.5% in patients with hepatic failure. Thus, even though Duzitol has longer half-lives in the presence of hepatic failure, the longer half-lives are meaningless because the "distribution" half-lives account for fully 99.5% of drug elimination in patients with hepatic failure. It is not until 6 h after a bolus that Duzitol concentrations are continuously lower in normal patients than in patients with hepatic failure.

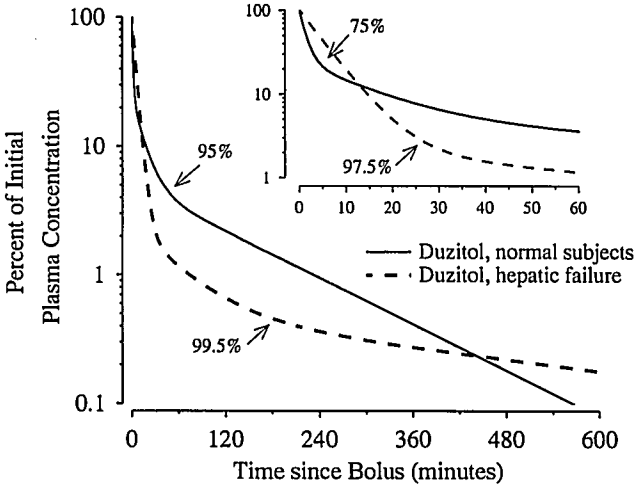

FIG. 2. Plasma Duzitol concentrations following a bolus dose, as a percentage of the initial concentration, in normal patients and patients with hepatic failure. The transition between the rapid and slow distribution half-lives can be seen on the inset (arrows), while the transition between the slow distribution and terminal elimination half-lives is most easily seen on the larger graph. The arrows show the percent decline achieved by the prior half-lives at each transition.

TABLE 2. Percent Coefficients of Each Half-life, Calculated from Table 1

	Duzitol		
	Normal Subjects	Hepatic Failure	Propofol: Normal Subjects
Rapid distribution	75%	97.5%	94.6%
Slow distribution	20%	2%	4.9%
Terminal elimination	5%	0.5%	0.57%

We can gain insight by recasting the three-compartment model in the more physiologic terms of volumes and clearances. Table 3 shows the volumes and clearances of Duzitol and propofol, also derived from the parameters in table 1. In subjects with hepatic failure, Duzitol has a very large slow compartment with a very slow clearance. The slow clearance to this large compartment permits it to act as a sink for the Duzitol. The drug concentration continues to rise in this compartment, even following very long infusions. This continued accumulation increases the rate of decline in plasma drug concentration when an infusion is terminated. More importantly, this peripheral sink releases drug very slowly back to the central circulation once the concentrations in the central circulation have fallen below the peripheral concentrations. Further insight into the complex relationships of volumes and clearances to recovery is provided by an excellent comparison with a hydraulic model by Hughes *et al.* The volumes and clearances of table 3 correspond to the cylindrical "bin" areas and conductances of the hydraulic model in their manuscript.

TABLE 3. Volumes and Clearances, Calculated from Table 1

	Duzitol		
	Normal Subjects	Hepatic Failure	Propofol: Normal Subjects
Volumes (l)			
Central	7.6	5.0	6.3
Rapid compartment	12	6	12
Slow compartment	46	82	266
Steady state	66	93	284
Clearances (l/min)			
Central	0.68	0.51	1.9
Rapid distribution	2.6	0.12	1.6
Slow distribution	0.79	0.20	1.8

As Hughes *et al.* point out, the "context-sensitive half-times" may not be relevant in some settings. Figure 3 shows a family of curves, representing the time required for the concentrations to decrease by percentages from 10% to 90%. If only a very slight decrease in concentration is required at the conclusion of an anesthetic, then the 10% curve, and not the 50% curve, would be relevant, and our hypothetical Duzitol might prove useful in long procedures.

In selecting an appropriate recovery curve, we are branching from a discussion of pharmacokinetics to an analysis which combines pharmacokinetics and pharmacodynamics. Such an analysis requires modeling the equilibration between the plasma and the site of drug effect, which also influences recovery time. Pharmacodynamic factors influencing the time to recovery also include the therapeutic plasma concentrations for specific degrees of drug effect, and the influence of concurrent disease and polypharmacy on the therapeutic windows. For example, if hepatic failure changes the decrease in Duzitol concentration required for emergence from 50% to 80%, then Duzitol becomes far less attractive in hepatic failure for strictly pharmacodynamic reasons. We have previously attempted to incorporate both pharmacokinetic and pharmacodynamic considerations into a discussion of opioid selection.[2]

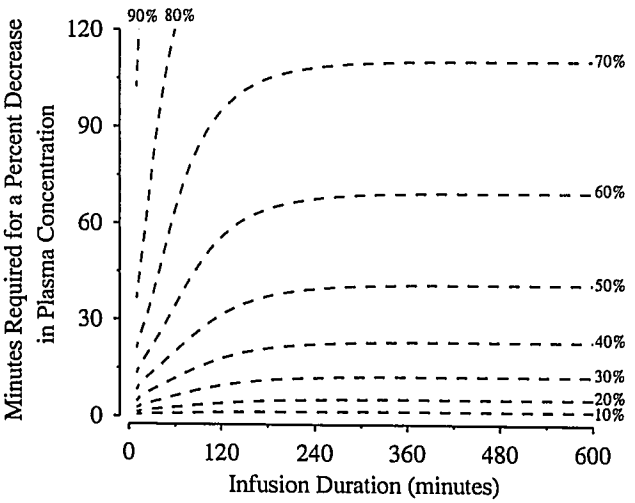

FIG. 3. Family of recovery curves for Duzitol in normal subjects showing the time to various percent decreases in plasma concentration following termination of a steady-state infusion. The 50% line is the "context sensitive half-time," where the context is the duration of the infusion (the x-axis).

Because the conventional method of reporting pharmacokinetic results, as shown in table 1, may not yield clinically interpretable conclusions, what should investigators report? First, they should still report the half-lives, volumes of distribution, and clearances, because these define the fundamental pharmacokinetic model. The percent coefficients, as shown in table 2, are also useful: if the percent coefficient of the terminal elimination half-life is very low, then the terminal half-life is probably clinically irrelevant. We should abandon drawing clinical conclusions from the half-lives of intravenous anesthetic drugs described by multicompartment pharmacokinetic models and start thinking of recovery times using computer simulations of specific clinical scenarios. The context-sensitive half-time, as described by Hughes *et al.* and also shown in figure 1, is one such simulation. We encourage reporting context sensitive half-times in pharmacokinetics research when a 50% decrease is clinically appropriate.

STEVEN L. SHAFER, M.D.
Assistant Professor of Anesthesia

DONALD R. STANSKI, M.D.
Professor of Anesthesia and Medicine (Clinical Pharmacology)

Stanford University School of Medicine and Palo Alto Veterans Administration Medical Center
Palo Alto, California

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