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Pitfalls in Deriving Pharmacokinetic Variables. III

To the Editor:—In a recent editorial on pharmacokinetic modelling of thiopental, Dr. Stansky[1] stated that pharmacokinetic parameters are useful in characterizing the rate and extent of drug distribution and elimination in an individual patient. While pharmacokinetic parameters such as distribution volumes, rate constants, half-lives, and clearances can be measured in an individual patient, in a certain sense it is doubtful that these parameters can be used to characterize a patient. As can be seen from the data of Morgan *et al.*[2,3] the pharmacokinetic parameters have a large intersubject variability. The standard deviations of the measurements in homogeneous groups of patients are for most parameters around 50 per cent of the mean or more. This large variability precludes some uses of these parameters. In particular, it is generally not possible to determine that an individual measurement is abnormal because the normal ranges are so large. In this sense one cannot use the pharmacokinetic parameters to characterize an individual patient. What can still be done is to compare groups of patients such as normal surgical patients and pregnant women during cesarean section as done by Morgan *et al.*[3] The origin of the large variability is certainly multiple, but it is likely that a large part of it is due to the approximate nature of the pharmacokinetic model. This variability is not peculiar to thiopental and has been observed in most pharmacokinetic studies. It renders unlikely that one will measure pharmacokinetic parameters to characterize an individual patient as one measures for example, arterial blood gases, *i.e.*, to determine if they are within the normal range or not.

DR. PH. MERTENS
Department of Anesthesia
Hopital Universitaire
St. Pierre
322 rue Haute, B-1000
Brussels, Belgium

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In reply:—Tanner has once again highlighted the importance of distinguishing between the elimination and distribution phases of the plasma time-concentration curve of a drug in order to calculate its elimination half-life. However, those interested in the derivation of pharmacokinetic variables should be well aware of this problem, which has been emphasized over the years (*e.g.*, Wagner[1]). The true elimination phase can be identified with reasonable certainty if the measured elimination half-life is small compared to the duration of data collection (ideally, not less than about five to seven elimination half-lives). This stipulation validates the accuracy of the pharmacokinetic variables calculated for thiopental in the two cited publications.[2,3] Furthermore, Tanner's

speculation that distribution of thiopental into fat may not be complete, even after 12 hours, is inconsistent with earlier recorded data. Serial biopsies of adipose tissues in humans enabled Shideman *et al.*[4] and Mark and Brand[5] to show that, contrary to findings in dogs, distribution of thiopental into human fat is complete within 2 hours of its administration. The discrepancy between predicted and observed times to equilibrium of thiopental in fat has not been addressed in available mathematic or computer models. (The question of direct intercompartmental diffusion from lean to adjacent adipose tissue, bypassing the limitations of tissue perfusion, has been raised[5] but not settled.) These comments illustrate a point made in Stanski's editorial[6]—that one limitation of physiologic modeling in human subjects is the large number of assumptions required.

Feingold notes that collection of pharmacokinetic data is facilitated by continuous drug administration. However a recent report by Stanski *et al.*[7] injects a note of caution in comparing studies of thiopental by infusion *vs.* single bolus doses. They found that following cessation of prolonged infusions of high doses of the drug, its elimination rate fitted a Michaelis-Menten rather than a first-order model. Such behavior was apparent in some subjects at plasma thiopental concentrations much lower than those observed by us,[2,3] where the elimination rate was clearly first-order. This suggests that thiopental pharmacokinetics may be influenced by the size of the dose and/or the duration of its administration.

There has been a trend recently away from model-dependent treatment of pharmacokinetic data.[8] Nevertheless, as Feingold indicates, assumptions are made in fitting plasma time-concentration data to a poly-exponential equation. Discussing these assumptions, Wagner,[9] suggested that values of elimination half-life, initial distribution volume, and volume of distribution at distribution pseudo-equilibrium calculated from the poly-exponential equation are truly model-independent. In contrast, values of volume of distribution at steady-state and of total body clearance assume an n-compartment mammillary model with elimination only from the central compartment.

Weiss and Förster[10] developed a method for calculating pharmacokinetic variables in terms of circulatory drug transport using the methods of linear systems theory. All the information required is given by the areas under the plasma concentration time curve and under the first moment of the curve, which provide model-independent values of volume of distribution at steady-state and total body clearance. The methods for calculating these two variables are identical with those used by Wagner[9]; thus validating our methods too as model-independent.

Finally, both Feingold and Mertens suggest that the large intersubject variability we reported[2,3] may have arisen from the mathematic analysis of the data. This is unlikely, since the analysis was independent of any pharmacokinetic model and also because in each subject, calculation of parameters by different methods gave similar results. For example, values of the area under the thiopental plasma time-concentration curve in the pregnant patients[3] do not differ significantly whether calculated by using the linear trapezoidal rule or by mathematic integration, *i.e.*, using the coefficients and exponents of the respective poly-exponential equations (paired t test, $P > 0.05$). The mean difference in area was 13.4 per cent and the range was 4.3 to 23.9 per cent. These relatively small differences can not account for the much larger intersubject differences reported.

DENIS J. MORGAN, PH.D.
Lecturer, Department of Pharmaceutics
Victorian College of Pharmacy

GRAEME L. BLACKMAN, PH.D.
Senior Lecturer, Department of Pharmaceutical Chemistry
Victorian College of Pharmacy

JOHN D. PAULL, M.B.B.S.
Director of Anaesthetics
The Royal Women's Hospital
Carlton, Victoria
Australia, 3053

LESTER C. MARK, M.D.
Fulbright Senior Scholar
Department of Pharmaceutical Chemistry
Victorian College of Pharmacy

381 Royal Parade
Parkville, Victoria
Australia, 3052

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In reply: Pharmacokinectic analysis in anesthesia certainly has captured the interest of anesthesiologists as judged by the volume of correspondence arising from two recent thiopental pharmacokinetic publications,[1,2] and an accompanying editorial.[3] A goal of pharmacokinetic data analysis is to use the drug plasma concentration *vs.* time curve to characterize the rate of drug elimination from the body (clearance) and the extent of drug distribution (volume of distribution). These are often the most important parameters with physiologic meaning that can be obtained from plasma concentration *vs.* time data. As Dr. Feingold indicates, there are many mathematical techniques available to characterize the plasma concentration *vs.* time curve and derive the pharmacokinetic parameters of clearance and volume of distribution. Polyexponential equations have the advantages of being mathematically simple, not requiring complicated analytical techniques for fitting, and are used easily to calculate clearance and volume of distribution. There is a large body of experience in their application to pharmacokinetic data analysis.

Drs. Feingold and Mertens are bothered by the large intersubject variability in the thiopental pharmacokinetic parameters. This large variability may be due to the quality of data collection and analysis. It may, however, reflect the true large variability that exists in human populations. Large variability has been shown to be true for theophylline clearance in patients.[4] Large intersubject variability decreases the utility of the population mean as a predictor for any one individual, requires that group sizes be larger to demonstrate statistical differences between different populations, and emphasizes the need for individualization of drug dosage.

I would like to correct a graphical oversight in the editorial figure.[3] The intercept of the distribution phase (A) line should be below the predicted drug plasma concentration at time zero. This correction is shown in figure 1.

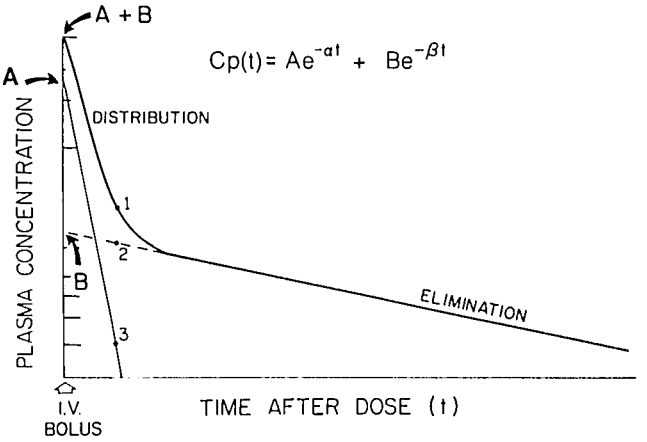

FIG. 1. To characterize the distribution phase it is necessary to subtract the concurrent and slower component of drug elimination. This is done by subtracting point 1 (plasma concentration observed on the distribution phase) from point 2 (corresponding plasma concentration on the extrapolated elimination phase line). The difference is plotted as a separate value, point 3. This feathering or residuals technique is done at several time intervals and a straight line drawn to characterize the residuals. The slope of this line represents the rate constant of the distribution phase (α).

DONALD R. STANSKI, M.D.
Assistant Professor of Anesthesia and Medicine (Clinical Pharmacology)
Stanford University Medical Center
Stanford, California 94305

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Another Warning Concerning the Hazards of Selector Shunt Values

To the Editor:—Hypoxic and barotrauma problems relating to the improper use of selector valves connecting ventilators to anesthesia gas machines continue to occur. Several reports of recent occurrences have been directed