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Pitfalls in Deriving Pharmacokinetic Variables. II

To the Editor:—The conclusion of Morgan *et al.*[1,2] that the half-life of a bolus dose of thiopental is longer than reported previously should come as no surprise to anyone familiar with the experimental descriptions of non-steady state drug administration and the pharmacokinetics of thiopental. As with many anesthetics, the distribution and elimination of thiopental may be nonlinear with important pharmacokinetic interactions occuring at low concentrations and long times. Thus, the results from any bolus study of thiopental would be incomplete, a problem which could be diminished not only by increasing the duration of sampling but also by increasing the duration of drug administration as with a continuous infusion or a series of bolus doses.

In his editorial in the same issue of ANESTHESIOLOGY, Stanski[3] emphasizes the advantages of pharmacokinetic as compared to perfusion models. However, he misses the point that not only does the selection of a theoretical model effect the mathematical analysis, but also the mathematical analysis effects the selection of a theoretical model. What are the implications of fitting the discrete thiopental concentration/time data to a poly-exponential equation? Why not use a polynomial, a power function or a Fourier integral?

By using a poly-exponential equation, Morgan *et al.* are led to the very questions which Stanski says they are trying to avoid. What are the number of compartments? What are their perfusions? What are the connections between the compartments, mammilary or catenary? This perfusion model mentality is inherent to their poly-exponential analysis and is demonstrated by the favorable comparison of their half-lives with those from the compartmental analysis of Ghoneim and Van Hamme.[4]

Putting aside these theoretical questions, let us look for any clinically relevant data about the use of thiopental for induction of anesthesia for cesarean section. I do not find it reassuring to learn that these seven obstetrical patients had an elevenfold variation in V_{ss}, a tenfold variation in Cl_p, and an eightfold variation in beta half-life. Did the large variability of these derived parameters result from their experimental design, their mathematical analysis, or from their inconsistent doses of thiopental? For example, Patient 10 weighed 53 kg and received a 350 mg bolus of thiopental, while Patient 7 who weighed 92 kg received a 300 mg bolus of thiopental.

Lastly, let me illustrate a clinical situation where the description of the differences between patients was facilitated by the administration of thiopental as a continuous infusion. The simplest description of these data

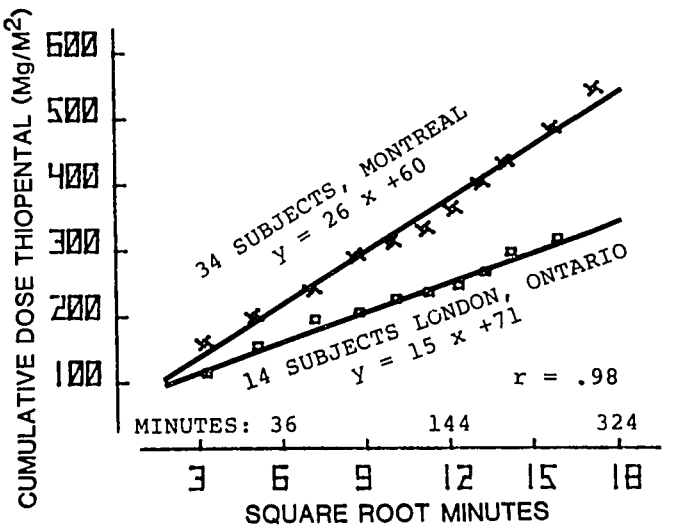

FIG. 1. Cumulative doses of thiopental required by two groups of patients studied by Kerri-Szanto and published by Eger.

(pharmacokinetic or emperic, depending on your inclination) relates the cumulative doses of drug to the square root of elapsed minutes and previously was used to characterize infusions of lidocaine,[5] *d*-tubocurarine, and pancuronium.[6]

Figure 1 shows the cumulative doses of thiopental required by two groups of patients studied by Kerri-Szanto and published in Eger.[7] The Xs and squares are the mean data of two groups from Montreal or London, Ontario. The discrete data are easily fitted to lines (r = 0.98), the equations for which appear adjacent to the lines. This simple description lacks the mathematical rigor of the methods used by Morgan *et al.* but seems to adequately describe the clinically relevant events when the only experimental data consists of time, drug dose, blood concentration, and/or pharmacologic effect. Furthermore, there is nothing in this analysis that prevents the derivation of the apparent volume of distribution or the elimination half-life.

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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.

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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

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