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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