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(Accepted for publication September 22, 1981.)

Anesthesiology
56:235, 1982

Pitfalls in Deriving Pharmacokinetic Variables. I

To The Editor:—The reports of Morgan *et al.*[1,2] and the editorial by Stanski[3] fail to emphasize several problems in deriving the rate of elimination of a drug from its plasma concentration *vs.* time curve.

One problem is that in analyzing the plasma concentration *vs.* time curve over several hours, it is not possible to distinguish between elimination or irreversible loss of the drug from the plasma, and distribution of the drug into tissues with especially long time constants. For instance, for thiopental assuming 75 per cent protein binding, 20 per cent of the body weight consisting of fat, a fat/blood partition coefficient of 11,[4] and 7 per cent of a 6 l/min cardiac output going to fat, the time constant for fat tissue would be approximately 22 hours. Ghoneim and van Hamme's[5] three-compartment model predicts that distribution will be complete in approximately 2.5 hours after the bolus administration. One may reasonably assume that after this time the distribution of thiopental into fat is not complete. In fact, it may not be complete at the end of their 12 hour data collection period; thus, the drug that goes to fat during this period appears to be irreversibly lost, that is, it appears to be excreted. A similar "overestimation" of the true elimination of other drugs used during anesthesia may be found if plasma levels of the parent drug can be determined for several days.

Another problem is that the model independent pharmacokinetic variables, clearance and apparent volume of distribution, are derived by integrating the plasma concentration *vs.* time curve from the time of drug administration to infinity. Obviously, the shorter the data collection period, the larger the possible error in the integration, and hence in these two variables.

Pharmacokinetic studies of drugs used during anesthesia in which data are collected for several hours are still quite useful to anesthesiologists because they do describe the amount of drug in the plasma, and presumably the rapidly equilibrating tissues during the course of the average anesthetic period. One must be aware that the shorter studies may overestimate the importance of drug elimination and underestimate the importance of drug distribution. Further studies are needed to attempt to correlate the variation in pharmacokinetic variables seen between individuals and variations in those factors which influence drug distribution such as cardiac output, degree of protein binding and regional blood flow.

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(Accepted for publication September 22, 1981.)