EDITORIAL VIEWS

How Far Can We Go With Compartmental Models?

HOMER and Stanski have previously observed that elderly patients require less thiopental than that required by younger patients to reach an EEG-based criterion of anesthetic onset.[1] However, the reasons for this difference have remained uncertain. This issue of ANESTHESIOLOGY contains two articles that apply pharmacokinetic modeling techniques to this difficult problem.[2-3] Both introduce new concepts that may leave clinical anesthesiologists puzzled, sceptical or both.

Apparent or Perfused Compartments?

Studies of drug disposition yield large quantities of concentration-time data that must be simplified by mathematical analysis. The most satisfying approach is to derive a physiological model that emulates, as far as possible, what actually happens in the body. Such a model may comprise a number of perfusion-limited compartments, each defined in terms of volume, blood-flow, and apparent tissue:blood partition coefficient λ_{TB}. The greater the number of identifiable compartments, the closer the model may be expected to emulate drug disposition in patients. An advantage of such models lies in their ability to account for hemodynamic changes such as altered cardiac output. They have one great drawback; numerical values must be assigned to their many parameters, and this may present an insuperable difficulty.

Alternatively, drug disposition may be represented by simple compartmental models whose volumes are "apparent" rather than "real." For instance, if the decaying drug concentrations after a single dose or infusion can be fitted by a function comprising the sum of two expo-

nential terms, a corresponding two-compartment model can be derived. This may have one of three forms (fig. 1) which are indistinguishable unless some *a priori* reasoning is applied to narrow the choice. For types A and B, standard equations permit calculation of V_1, k_{12}, and k_{21}. However, there are innumerable feasible solutions for type C because there are too many unknowns in the equations.

A more complex model (with three or more compartments) may be proposed, but should be preferred only if it can be shown that it has a greater statistical likelihood of representing the original data source than the simpler alternative. The more complex the model the more parameters it will have, and the greater the uncertainty will be in identifying them.

What is the relation between the compartmental volumes obtained by these two modeling approaches? One of the "perfused" compartments in a physiological model might have a physical volume $V = 10\ l$ and tissue:blood partition coefficient $\lambda_{TB} = 5$. From a functional standpoint, this behaves exactly as if it were a 50-l volume with $\lambda_{TB} = 1$. Thus, the product $V \cdot \lambda_{TB}$ in such a model represents a "drug space" that is analogous to the apparent volume in a compartmental model. Indeed, the sum of all such spaces should approximate to Vd^{ss}, the apparent volume of distribution at steady state.

Elimination and Transfer Clearance

If it is assumed that linear kinetics apply to a compartment from which the drug is eliminated, the efficiency of this process can be defined as the rate of elimination per unit concentration. Thus in a perfused compartment having input and output concentrations C_a and C_v and perfusion Q:

$$Cl = \frac{Q(C_a - C_v)}{C_a} \tag{1}$$

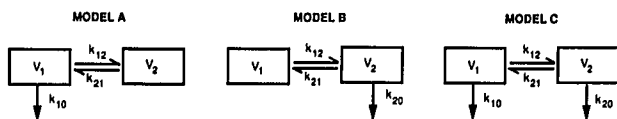**MODEL A**   **MODEL B**   **MODEL C**

FIG. 1. From any biexponential decay curve, there are three equally feasible two-compartment models.

In an apparent compartment, a similar principle applies. Thus if dC/dt is the rate of change in concentration at any time:

$$Cl = \frac{V \cdot dC/dt}{C} \tag{2}$$

Since a rate constant can be defined as $\frac{dC/dt}{C}$ it follows that:

$$Cl = V \cdot k \tag{3}$$

V has the dimension volume and k the dimension 1/time, so clearance must be volume/time. This is consistent with the traditional definition, based on the perfusion concepts shown in equation 1 as the volume of blood cleared of drug per unit time. Since Cl indicates the rate of drug movement for a given concentration gradient, we can extend this concept to include intercompartmental transfers. For instance, it can be shown that for any real model of type A:

$$V_1 \cdot k_{12} = V_2 \cdot k_{21} \tag{4}$$

Since each term is the product of a volume and the rate constant describing drug loss from that volume, it is a clearance. Thus while $V_1 \cdot k_{10}$ describes the elimination clearance Cl_{10}, $V_1 \cdot k_{12}$ is the intercompartmental, or transfer clearance Cl_{12}.

Parametric and Nonparametric Effect-Compartment Modeling

Effect-compartment modeling is a familiar concept to most anesthesiologists. However, the distinctions between parametric, semiparametric, and nonparametric modeling are not so well established and the nomenclature has become a minefield. If serial plasma concentrations of almost any drug are plotted against simultaneously determined measurements of pharmacologic effect, a hysteresis curve results (Stanski and Maitre,[3] fig. 1). The problem can be overcome by adding an "effect" compartment whose rate constants are adjusted until the concentrations in that compartment, when plotted against effect, show minimal hysteresis.[4,5] From such a plot we can determine Cp^{ss}_{50}, the steady-state plasma concentration associated with 50% of the maximum possible effect. Although Sheiner described this as a nonparametric model,[5] it is better to use the term "semiparametric," in that the pharmacokinetic

model is fully described by parameters but the concentration:effect function is unspecified. It also distinguishes this from his later method,[6] also described as nonparametric.

In a parametric model, the investigator decides in advance what function shall govern the concentration:effect relationship. For instance, Sheiner's model for d-tubocurarine[7] specified a "sigmoid E_{max}" function, whose parameters were then determined as part of the fitting process.

Nonparametric models make no assumptions at all about the pharmacokinetic model or the concentration: effect function.[6] The only assumption is that the effect-compartment concentration lags behind that in plasma according to a rate constant k_{eo}. By this means, effect-hysteresis can be eliminated before the model-identification process begins. En passant, it should be noted that the technique used here by Stanski and Maitre,[3] described as "semiparametric," is in fact Sheiner's nonparametric method.[6]

Population Pharmacokinetics

In a typical pharmacokinetic study, compartmental models derived from one group of subjects are compared with those from another. Each model parameter is averaged by groups, and the means ($\pm$SE) are then used to compare the groups with each other. Since each parameter is itself an estimate with unknown variance, this procedure is fraught with error. To make matters worse, factors such as age, weight, and sex may be correlated, so that their influences may be difficult to establish.

Using any number of raw data sets, and regarding external factors as parameters to be included in the regression procedure, Beal and Sheiner's computer program NONMEM not only determines a "population model" for the drug, but also determines which external factors have significant influences.

A NONMEM Approach to the Aging Problem

Stanski and Maitre[3] analyzed 16 data sets from patients given rapid infusions until their EEGs became isoelectric, and 48 from subjects given a variety of bolus iv doses. NONMEM analysis of data from subjects given bolus iv doses showed that compartmental modeling was impossible. Figure 2 of their article shows why: some concentration curves fell rapidly in the first 3 min, while some remained almost unchanged and others even increased! When the infusion results were included, the data could be analyzed in terms of a three-compartment open model. The initial distribution volume and plasma clearance were both correlated with body weight, while k_{12} correlated with age.

In a second analysis they derived one-compartment models from data restricted to a 10-min period after the short infusions. As expected, the distribution volume Vd was similar to V_1 in the three-compartment model. "Elimination" from such a single compartment must be due to both metabolism and distribution, but since thiopental has low hepatic extraction, distribution can safely be regarded as the major contributor. NONMEM analysis showed that the elimination rate constant decreases with age, but also varies inversely with the apparent volume of distribution. NONMEM analysis of the pharmacodynamic data confirmed their earlier finding[1] that Cp^{ss}_{50} does not vary with age.

Because the data derived from "bolus" patients proved impossible to analyze, they concluded that early plasma concentration data following bolus doses of thiopental must be viewed with caution. I concur. Since thiopental is subject to significant uptake during the "first pass" through the lungs,[8–10] occasional arterial samples taken during the first 2–3 min after an iv bolus dose may encounter the delayed and slurred thiopental peak at any point,[9] leading to some odd results indeed. It follows that any model for early distribution that depends upon an assumption of immediate central compartment mixing is ill founded.[11] Stanski and Maitre suggest that their short (2–3 min) infusion may have resolved this difficulty by minimizing the "first-pass" effect. We should note that these were the very conditions under which the age effect was observed—an added attraction.

What can we conclude from this complicated study? First of all, it is clear that the age effect is pharmacokinetic, not pharmacodynamic in origin. However, the kinetic data are difficult to interpret. Although the 16 "bolus" patients yielded inconsistent plasma concentrations during the first 3 minutes—so much so that compartmental analysis was impossible—we are asked to believe that the addition of 48 "infusion" data sets allowed three-compartment population models to be derived, with reduced values of k_{12} in elderly patients. In view of the extreme variability of the initial values in "bolus" patients, I find this hard to accept. Indeed, we must wonder, in the face of their own misgivings, why the authors did not disregard the data from those subjects. The one-compartment analysis of early data (from "infusion" subjects only) was more convincing, and showed a significant relation between k_e and age.

The authors claim to have demonstrated a reduction in intercompartmental clearance with increasing age in both one-and three-compartment models. In the three-compartment model, intercompartmental clearance would be represented by the product $V_1 \cdot k_{12}$, and in the one-compartment model, by $V_1 \cdot k_e$. In fact, we are offered no information on either of these derived quantities.

Since V_1 in the three-compartment model shows high variability, and in the one-compartment model is negatively correlated with k_e, a demonstration of age-related changes in k_{12} and k_e is not quite enough.

The "Concurrent ICG" Model for Thiopental

Henthorn et al. proposed that the early disposition of thiopental might be defined more precisely by considering the concurrent disposition of an intravascular marker such as indocyanine green.[12] They showed that the disposition of ICG follows two-compartment kinetics, with a small central compartment whose volume corresponds closely with that of the "fast circulation" blood volume. During the first few minutes after injection this equilibrates with a larger "slow circulation" blood volume, from which elimination may be assumed to occur. They suggested that by administering ICG and thiopental concurrently, common values for initial distribution volume V_1 and intercompartmental clearance Cl_{12} might be determined for the two substances. Using this principle, they derived a four-compartment thiopental model with elimination from V_2 (Avram et al.,[2] fig. 1). This new thiopental model has a significantly smaller central volume ($V_1 = 3.2$ l) than that derived by conventional three-compartment modeling.[1,3]

But is their model valid? Can the combined thiopental-ICG estimates of V_1 and Cl_{12} be used as parameters of the thiopental model? If we could be sure that the body treats ICG and thiopental identically during the initial distributive period, then perhaps we might. However, thiopental partitions into lung tissue whereas ICG does not. So, unless the patient has no lungs we cannot assume that thiopental and ICG share identical central distribution volumes.

We then have the problem of V_2, representing a "slower" blood volume (3.8 l) in the ICG model but unconstrained (30.4 l) in the thiopental model. This may be considered from two points of view. In compartmental terms, it can be argued that if Cl_{12} is assumed to be the same in both models, then the volume (V_2) to which that clearance applies should also be the same. However, a more physiological approach might argue that assuming perfusion-limited kinetics, Cl_{12} and $V_{2(ICG)}$ define the "perfusion" of compartment 2 in the thiopental model, while the other 26.6 l represent instantly equilibrating "tissue." While superficially attractive, this concept transforms the compartmental model into an entirely new, quasi-physiological entity. Unfortunately, the authors offer little evidence that this new creature is any more "likely" than a simpler alternative. In view of the well-known dangers of ascribing physiological significance to compartmental model parameters,[13] we should not be beguiled too easily.

Application of the "Concurrent" Model to the Problem of Aging

Avram et al.[2] applied this technique to patients whose ages ranged from 20–80 yr. Their results suggest that the central volume V_1 does not vary with age, but that the intercompartmental clearance Cl_{12}, decreases with age. However, we should note that both these parameters have values close to those for ICG alone, and owe little to the thiopental data. The only other pharmacokinetic correlate was the steady state volume of distribution, but this could not possibly be significant so far as early phase kinetics are concerned.

In addition to my doubts regarding the model itself, I am concerned that all the subjects were heavier than might be expected, yet there is no indication as to whether patients (especially the young men) were obese office workers, weightlifters, or simply big. Moreover, the study seeks to establish why aging influences the dose requirement for thiopental, but makes no attempt to confirm that the effect was actually demonstrable in the subjects studied. In consequence, the authors are left wondering whether they were, after all, pursuing a chimera.

It is interesting to note that both studies, despite very different approaches and a number of limitations, have arrived at substantially the same conclusions. First, that the efficiency with which thiopental distributes from the central circulation to the "well-perfused" periphery diminishes with increasing age. Second, that body weight is a poor predictor of thiopental kinetics. The physiological basis of the age effect has yet to be elucidated, although the ICG data do suggest that hemodynamic differences may be involved.

So far as induction of anesthesia is concerned, the implication is clear: reduced intercompartmental clearance means that the induction dose remains longer in the central compartment, and so the mass of drug available to the brain is correspondingly greater. It follows that the age effect will be more evident when thiopental is administered as a short infusion than when given as a bolus.

What Next?

It is evident that so far as the early distributive period is concerned, the assumptions underlying the simple compartmental model render it quite inappropriate as an investigative tool. To overcome some of these limitations, Henthorn's group have developed an ingenious hybrid model which incorporates some physiological features. However, it cannot account properly for the complexities of early distribution and makes no attempt to represent the dynamics of pharmacological effect.

In fact, there is no reason why their model should not

be developed to account for pulmonary uptake and real values of cardiac output: as Taeger et al. have shown,[14] an ICG marker provides all the necessary information. Given serial estimations of both arterial and mixed venous thiopental concentrations, it then becomes possible to identify a perfusion model that can account for both pulmonary uptake and early distribution. Such a model might then be able to elucidate the influence of age upon thiopental kinetics in proper physiological terms.

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