cause of the extremely low overall coefficient of variation. The variation, including assay variation and intra- and intersubject variations, for the prednisone data was 15%. A statistically significant difference was found between the two treatments according to prednisolone data as well. Again, even though the observed difference was only 8% between the two treatments, significance was established and was attributed to the excessively low overall coefficient of variation (12%). The combined prednisone–prednisolone areas under the serum concentration–time curves were not different between the two treatments.

There was a consistent difference between treatments by both methods of analysis. However, the amount of synthetic steroid available following each treatment was essentially the same. Prednisolone was always present in larger quantities than was prednisone, regardless of the drug administered. The relative levels of prednisolone to prednisone, prednisolone to administered drug, and prednisone to administered drug in serum were dependent on which drug was administered. Contrary to previously published studies (8–11), prednisone areas under the serum concentration–time curves were greater following prednisone administration than they were after prednisolone administration, while prednisolone areas were greater following prednisolone treatment than they were following prednisone administration. The predominating steroid in serum was prednisolone, even though the relative serum levels were dependent on the administered drug.

Although there were statistically significant differences under the serum concentration–time curves between the two treatments, the therapeutic significance is difficult to assess. Both of these anti-inflammatory steroids are used on a chronic multiple-dose basis. The clinician establishes the dosing regimen by titrating the dose to a therapeutic end-point, *i.e.*, remission of symptoms. Even if these results were confirmed in humans, it would be difficult to establish that an 8 or 13% difference in total area under the serum concentration–time curve would actually be significant in the clinical situation.

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Nonlinear Pharmacokinetic Model of Intravenous Anesthesia

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Abstract □ A nonlinear pharmacokinetic model was constructed to describe the body distribution of intravenous anesthetics, using the physiological modeling approach for drug distribution kinetics. The model considers the physiological parameters of tissue volumes and blood flow rates for the standard four phases of blood, viscera, lean tissue, and adipose tissue and also the associated drug parameters known to influence drug distribution. A simple ramp function having a characteristic time (volume per flow rate) is used to describe the rate of approach to equilibrium conditions for each tissue phase. The model was evaluated for the distribution of methohexital and thiopental by comparing calculated values to experimental drug concentrations taken from the literature. The physiological alteration of obesity also was programmed into the model to evaluate its capability for predicting the influence of body alterations on drug distribution. The results indicated that a preliminary mathematical model of relatively simple design is capable of at least a semiquantitative prediction of intravenous anesthetic drug concentrations in body tissues and has the potential of accounting for differences in drug distribution in the presence of selected physiological alterations.

Keyphrases □ Anesthesia, intravenous—distribution, nonlinear pharmacokinetic model described, methohexital and thiopental □ Pharmacokinetic models, nonlinear—described for intravenous anesthetics methohexital and thiopental □ Distribution, drug—intravenous anesthesia, nonlinear pharmacokinetic model described

Induction, maintenance, and recovery during intravenous anesthesia are dependent upon the amounts of anesthetic agent within the brain tissues after dosing and are functions of the amounts of drug in the plasma. Alterations in body distribution processes controlling drug levels in the brain and plasma can influence the dosages required for anesthesia and may explain many ineffective dose regimens for these drugs.

Clinical use of methohexital and thiopental for anesthesia in dental patients has indicated some conditions that can alter the tissue levels of these anesthetics to result in enhanced potency or prolonged narcosis after normal induction doses. These conditions include dehydration (1), uremia (2), peripheral circulatory failure (2), increased cardiac output (2), electrolyte disturbances (2), hepatic failure (2), and chronic renal failure (3).

Attempts have been made to describe the pharma-

cokinetics of intravenous anesthetics to predict the effects of altered body distribution processes on subsequent tissue levels. Gibaldi *et al.* (4) described the body distribution of thiamylal, ketamine, and phencyclidine according to the compartmental analysis presented by Wagner (5). Ketamine and phencyclidine were described according to a one-compartment open model and thiamylal according to a two-compartment open model.

Another model described thiopental pharmacokinetics according to blood flow rates and the relative mass for various tissues (6). The drug concentrations predicted by the model in blood and fat tissues 25 min after a single intravenous dose compared favorably with those measured directly in a patient. Quantitative predictions of the effect of liver metabolism of thiopental on its rate of disappearance from plasma were reported using a similar pharmacokinetic model (7). This model suggested that an inhibition of liver metabolism of the drug would prolong the duration of anesthesia. It was also used to suggest that an increase in hepatic drug clearance would simultaneously decrease brain concentrations (8).

Bischoff and Dedrick (9) devised a more elaborate model, which included flow limitations, lipid solubility, protein binding, and metabolism, to make *a priori* predictions of the distribution of thiopental in four body regions: blood, viscera, lean tissue, and adipose tissue. Absolute values were obtained for drug concentrations *versus* time and were compared with literature data of thiopental distribution in dogs and humans. Subsequently (10), they expanded their analysis, using additional body regions, to study the effects of intravenous injections of methotrexate in mice. Although certain discrepancies did exist, overall prediction of trends was correct.

These findings seem to be consistent with evidence that pharmacokinetic models can be used to predict dosage adjustments in various therapeutic situations (11–13). Also, much clinical evidence supports the belief that past dosing problems experienced with methohexital and thiopental can be anticipated with other drugs used in intravenous sedation techniques in dentistry. Therefore, sufficient justification exists to investigate the applicability of pharmacokinetic modeling of some of these drugs in predicting dosage adjustments and the time course of action in specific therapeutic situations. Of particular concern was the development of an appropriate model to predict the recovery time phase of drug action in view of the wide use of intravenous sedation and anesthesia in ambulant patients undergoing dental procedures.

The results indicate that a preliminary mathematical model of relatively simple design is capable of at least a semiquantitative prediction of drug concentrations in body tissues after intravenous dosing and can account for hypothetical differences in drug distribution in the presence of a select physiological alteration.

METHODS

Model Structure—The model can be thought of as an interactive blood–drug–tissue system. The body is assumed to consist of a single compartment having an aqueous phase, blood, and three tissue types (visceral, lean, and adipose) into which a drug can distribute. Features common to each type of tissue are a volume and a rate at which blood flows through it. These are denoted as V_sQ_s, V_lQ_l, and V_pQ_p for visceral, lean, and adipose tissues, respectively. The ratio of volume to rate establishes an estimate of the time required for equilibrium conditions to be achieved between the blood and the corresponding tissue.

The chief characteristic assigned to the blood is homogeneity; that is, the drug concentration in the blood is uniform throughout all blood vessels and tissues. Another feature assigned to the blood is the reversible binding of the drug to plasma protein. The fraction of drug in the blood that is not bound to protein is denoted by $f_1 = C_b{}^f/C_b$, where $C_b{}^f$ is the free concentration and C_b is the total concentration of drug in the blood. Of the free portion, some is ionized according to drug pKa and blood pH. The ionized fraction is denoted by $f_2 = C_b^{\text{ionized}}/C_b{}^f$. The effective free concentration is the nonionized free concentration, $(1 - f_2)C_b{}^f$, which is denoted by C^*. The fraction of drug reversibly bound to plasma protein at equilibrium is given by the nonlinear relationship:

$$C_b{}^b = C^*K_bB_b/(1 + C^*K_b) + C^*K_b'B_b'/(1 + C^*K_b') \quad \text{(Eq. 1)}$$

assuming two different families of binding sites as described by Gillette (14). Here the total concentration of drug in the blood is $C_b = C_b{}^f + C_b{}^b$, the sum of free and protein-bound drug; B_b and B_b' are the numbers of the two types of binding sites per liter of blood; and K_b and K_b' are the corresponding association constants, having the dimensions of inverse concentration.

A feature common to the lean and visceral tissues is that drug absorption from the blood follows a reversible protein binding relationship identical in form to Eq. 1. For lean tissue:

$$C_l = f_lC^*K_lB_l/(1 + C^*K_l) + f_lC^*K_l'B_l'/(1 + C^*K_l') \quad \text{(Eq. 2)}$$

where C_l is the drug concentration in the lean tissue, C^* is the effective free concentration of the drug in blood, B_l and B_l' are the numbers of binding sites per liter of tissue, and K_l and K_l' are the corresponding association constants. The fraction f_l describes the rate of approach to equilibrium. For this model, f_l is taken to be a simple ramp function of the characteristic time V_l/Q_l. The form of f_l is illustrated in Fig. 1. Similarly, in the visceral tissue:

$$C_s = f_sC^*K_sB_s/(1 + C^*K_s) + f_sC^*K_s'B_s'/(1 + C^*K_s') \quad \text{(Eq. 3)}$$

where the notation is as in Eq. 2 and f_s is a simple ramp function that reaches unity at time V_s/Q_s.

A feature unique to the visceral tissue is liver metabolism. This process is accounted for by assigning a separate flow rate, Q_r, through the liver. Obviously, Q_r is some fraction of Q_s. A reaction rate constant, K_r, is then assigned to describe what fraction of the available drug passing through the liver, *i.e.*, C^*Q_r, is metabolized. If the amount metabolized is denoted by A_r, then:

$$dA_r/dt = C^*Q_rK_r \quad \text{(Eq. 4)}$$

The adipose tissue absorbs drug from the blood according to the drug's lipid solubility. The average concentration of drug, C_p, in lipid cells at equilibrium is related to the free concentration in the blood through the lipid solubility, K_p, customarily defined as $K_p = C_p/C_b{}^f$. The concentration C_p at any time is assumed to be:

$$C_p = f_pK_pC_b{}^f \quad \text{(Eq. 5)}$$

where f_p is a ramp function of the type shown in Fig. 1 and has the characteristic time V_p/Q_p.

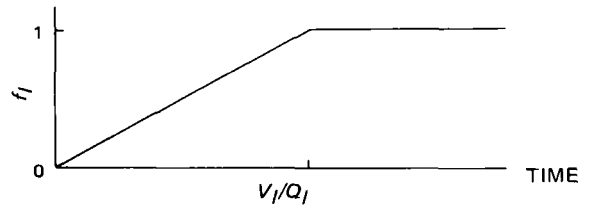

Figure 1—*Simple ramp function having a characteristic time (volume per flow rate) used to describe the rate of approach to equilibrium in the different tissue phases. The specific illustration is for the lean tissue, but similar ramp functions having correspondingly different characteristic times are used for visceral and adipose tissues.*

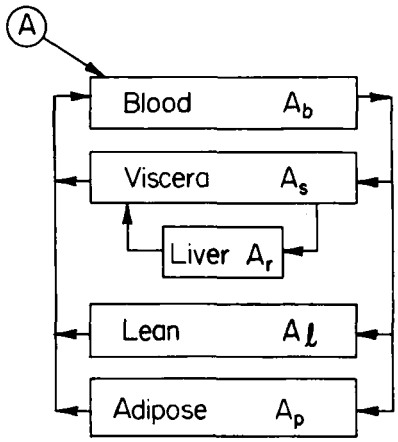

Figure 2—*Schematic representation of the present model: distribution of an initial amount of drug* (A) *to blood and tissue phases after initial dosing.*

For an initial drug dosage of amount A, the amount A_b remaining in the blood at any subsequent time is a function of the amounts of drug existing in the visceral tissues (A_s), lean tissues (A_l), and adipose tissues (A_p) and the amount metabolized by the liver (A_r) (Fig. 2).

The amount A_b at any time is found from the relationships describing amounts in other tissues:

$$A_s = C_s V_s \quad \text{(Eq. 6)}$$

$$A_r = \int_0^t (dA_r/dt)\, dt \quad \text{(Eq. 7)}$$

$$A_l = C_l V_l \quad \text{(Eq. 8)}$$

$$A_p = C_p V_p \quad \text{(Eq. 9)}$$

and the conservation relationship:

$$A_b = A - A_s - A_r - A_l - A_p \quad \text{(Eq. 10)}$$

Thus, the concentration of drug in the blood at any time is:

$$C_b = A_b/V_b \quad \text{(Eq. 11)}$$

Since Eq. 7 is merely a restatement of Eq. 4, it is clear that Eqs. 1–11 form a set of 10 simultaneous equations with the 10 variables C_b, $C_b f$, C_l, C_s, C_p, A_s, A_r, A_l, A_p, and A_b. These equations are fairly complex but can be easily handled by a computer.

The computer program[1] to solve this system of equations is written in CSMP (15, 16). This language is particularly convenient for investigating the time-dependent response of systems and has three built-in features useful in the present application. The special call LIMIT provides the ramps f_l, f_s, and f_p. The special call INTGRL integrates the differential Eq. 4 using a standard Runge–Kutta technique (17). The special call IMPL solves the simultaneous equations by a simple technique of successive approximations (17).

Parameters—Initial computer studies were performed on the distribution of methohexital and thiopental. Table I shows the physicochemical parameters and Table II shows values of tissue volumes, *etc.*, for a 70-kg man. The binding site concentrations and association constants are shown in Table III. Binding site concentrations are for the binding of thiopental by bovine albumin. It was assumed that these values, determined by Goldbaum and Smith (20), were appropriate for the binding of both thiopental and methohexital by plasma protein. These investigators also gave corresponding association constants for thiopental, but their values were somewhat at variance with the values of f_1 cited in Table I. Hence, the procedure adopted for determining the association constants shown in Table III was to: (*a*) select the first (K) on the basis of the results of Goldbaum and Smith and (*b*) calculate the second (K') using Eq. 1 and the corresponding values of f_1 from Table I for methohexital and thiopental.

Table I—Physicochemical Values for Methohexital and Thiopental (18)

Parameter	Methohexital	Thiopental
Protein binding, unbound fraction of drug in plasma, f_1	0.27	0.25
Ionization:		
pKa	7.9	7.6
Fraction of unbound drug ionized at pH 7.4, f_2	0.24	0.39
Lipid solubility, K_p	65	89

Table II—Values of Parameters Used to Describe the Four-Phase Model of the Blood–Tissue System for a 70-kg Man (19)

Tissue Volumes	Liters
Blood, V_b	5.4
Viscera, V_s	6.2
Lean, V_l	39.2
Adipose, V_p	12.2
Blood Flow Rates in Tissues	**Liters per Minute**
Viscera, Q_s	4.08
Lean, Q_l	1.28
Adipose, Q_p	0.26
Liver, Q_r	1.50

Since no corresponding data were available for visceral and lean tissues, the values B_s, B_s', . . . , K_l, K_l' remain as adjustable parameters in the model. In the calculations, these parameters are given the values listed in Table III. All remaining parameters are given in Table IV.

Results from a study of rats[2] indicated that the effective blood flow rate for adipose tissue may be similar to that for lean tissue in contrast to the value $Q_p = 0.26$ given in Table II. The plausibility of this postulate can be advocated from consideration of the usual interpenetrating configuration of adipose and lean tissues. The effective flow rate for the adipose tissue is the rate at which drug is made available for lipid dissolution. Thus, it may be that blood is brought to the lipid cells mainly through lean tissue "channels" so that the drug absorption rate is fixed by Q_l rather than by the flow rate Q_p. Consequently, two separate cases are treated in the initial calculations that follow; one is identified as $Q_p = 0.26$ (the Table II value) and the other is defined as $Q_p = Q_l$.

RESULTS

An initial goal of this study was to compare results calculated using the foregoing model to experimental drug concentrations, determined by Sunshine *et al.* (21), for methohexital. Such comparisons would be meaningful only at times for which the drug is relatively uniformly mixed in the blood. For example, the maximum blood concentration for the present model is A/V_b and occurs at time zero because of the assumed homogeneity of the blood compartment. Sunshine *et al.* (21), however, showed concentrations increasing from zero to values sub-

Table III—Values of Protein Binding Site Concentrations and Corresponding Association Constants[a]

Parameter	Value
B	870 mg/liter
B'	52 mg/liter
K	1.2×10^{-3} liters/mg
K' Methohexital	3.3×10^{-2} liters/mg
K' Thiopental	3.9×10^{-2} liters/mg

[a] From Ref. 20

[1] A listing of the program is available on request.

[2] To be published.

Table IV—Values of Remaining Parameters Used in the Present Calculations

Parameter	Value
Liver metabolism, K_r	1.0
Initial dose rate, A	2 mg/kg
Variations used in simulation of obesity:	
V_p	75.2 liters
Weight	140 kg
A (first computation)	1 mg/kg
A (second computation)	2 mg/kg

stantially larger than A/V_b during the 1st min after the start of injection. Therefore, it is conjectured that this elementary model is necessarily restricted to describing redistributions at times greater than the time in which the concentration of drug in the blood becomes relatively uniform. Based on the parameters, the calculations, and the cited experimental results, this restriction seems to be at times greater than approximately 1 min.

Figure 3 shows the calculated variations of methohexital concentration in the blood of a 70-kg man as a function of time for the two cases $Q_p = 0.26$ and $Q_p = Q_l$. The initial dosage was taken as 140 mg or 2 mg/kg. The values observed by Sunshine *et al.* (21), shifted (arbitrarily) by 1 min on the time scale, also are given. On this basis, calculated results are in fair agreement with the experimental observations.

The two sets of calculations, however, differ noticeably. The experimental data fall mainly between the two calculated curves and decidedly nearer the case $Q_p = Q_l$. The difference in drug concentration shown in Fig. 3 for the two cases is more predominant in the results for the visceral and adipose tissue concentrations (Figs. 4 and 5). Thus, a selection probably can ultimately be made between these two cases based upon experimental measurements of tissue concentrations.

Both the concentration and total amount of drug in lean tissue is never very large according to the model. Also, according to the calculations, the total amounts of methohexital metabolized during the 1st hr after injection are: (*a*) $Q_p = 0.26$, $A_r^{60} = 28$ mg or 20% of A, the administered dose; and (*b*) $Q_p = Q_l$, $A_r^{60} = 15$ mg or 11% of A.

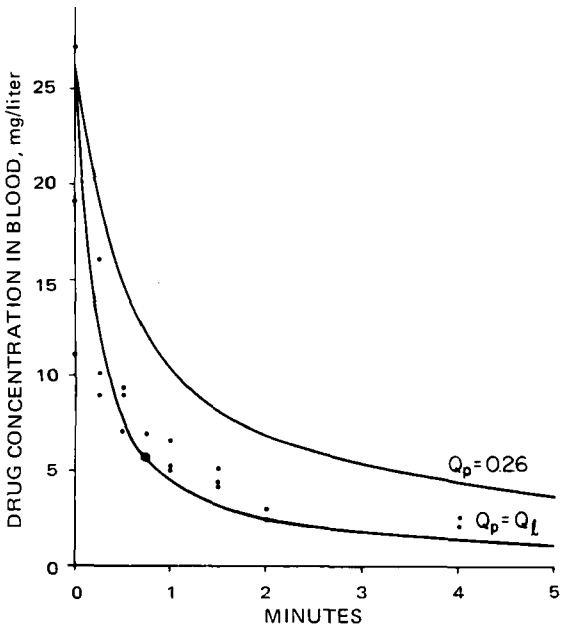

Figure 3—*Methohexital concentration in the blood* versus *time, calculated according to the model for the two cases* $Q_p = 0.26$ *and* $Q_p = Q_l$. *Curves denote calculated values; points are comparable experimental results (21).*

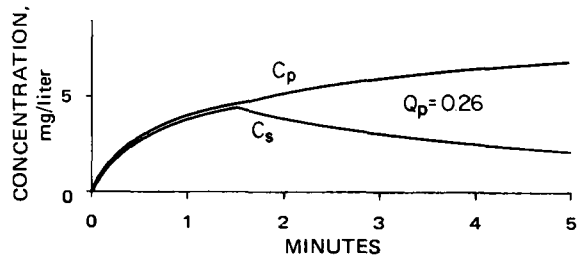

Figure 4—*Methohexital concentrations in adipose and visceral tissues* versus *time, calculated according to the model for the case* $Q_p = 0.26$.

In calculating the effect of liver metabolism, K_r was assumed to have the value of unity. Because the rate of metabolism is proportional to the nonionized free blood concentration, it varies as the blood concentration changes. Therefore, the rate in the model is greatest immediately following intravenous injection when the serum concentration is greatest. Subsequently, the metabolic rate decreases as drug is transferred from the blood to the tissue phases. Ultimately, most drug is stored in adipose tissue from which it slowly returns to the bloodstream and is metabolized by the liver. These calculated results for methohexital metabolism are in general agreement with the experimental observations of Brand *et al.* (18).

Figure 6 shows results calculated for thiopental using the parametric changes indicated in Tables I and III and restricted to the one case $Q_p = 0.26$. When comparing these results to the same case for methohexital, the differences to be noted are: the concentration of drug in the blood decays somewhat more rapidly for thiopental than for methohexital, the adipose tissue concentration is slightly higher for thiopental, and the peak visceral tissue concentration is 21% less for thiopental for the same initial dosage.

For the same liver reaction rate constant, $K_r = 1$, the amounts of thiopental metabolized are decidedly less than methohexital at corresponding times, *e.g.*, 14% of the administered dose during the 1st hr after injection with thiopental compared to 20% with methohexital. This finding also is in general agreement with the experimental observations of Brand *et al.* (18).

The effect of obesity was studied using the present model. In the absence of direct experimental data, it was decided to represent the hypothetical obese subject in the following way. The sum of phase volumes for the normal 70-kg man is 63 liters according to Table II. It was assumed that an obese subject had twice the normal weight—*viz.*, 140 kg, and twice the normal volume. It was further assumed that the entire added volume, 63 liters, was additional adipose tissue so that V_p has the value (12.2 + 63 =) 75.2 liters for the obese subject.

The effect on the obese subject of the same total initial dose of methohexital as used in the previous calculations for a normal subject, 140 mg, was computed. The peak value of drug concentration in the visceral tissue was the same in both calculations, but the subsequent decrease in visceral concentration was more rapid in the obese computation for both $Q_p = 0.26$ and $Q_p = Q_l$. Next the two subjects were compared on the basis of a total initial dose of 2 mg/kg, so the obese subject received 280 mg. This dose produced a peak concentration

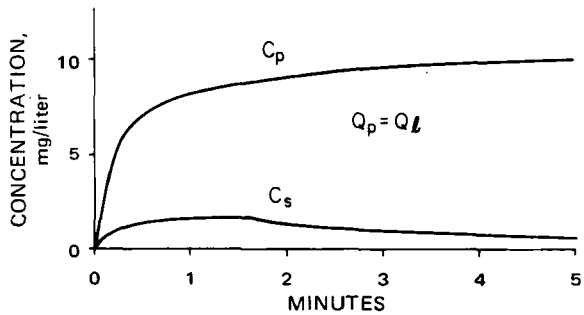

Figure 5—*Methohexital concentrations in adipose and visceral tissues* versus *time, calculated according to the model for the case* $Q_p = Q_l$.

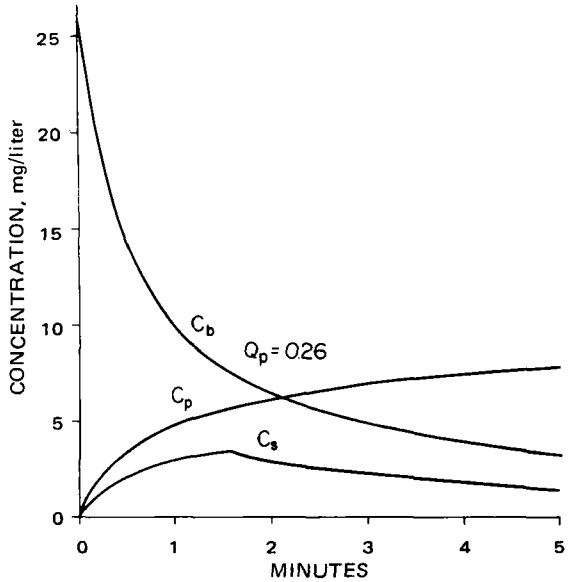

Figure 6—*Thiopental concentrations in blood, adipose tissue, and visceral tissue, calculated according to the model for the case* Q_p = *0.26.*

in the visceral tissue that was twice the previous value, again for the two cases of effective adipose tissue flow rates.

DISCUSSION

The described model is of the generalized nonlinear type discussed by Wagner (22), using the physiological modeling approach for drug distribution kinetics. The physiological parameters and the physicochemical drug parameters required by the model are similar to those used by Bischoff and Dedrick (9). Differences exist from their model, however, primarily in the fundamental assumptions made and in the manner of incorporating time dependence early in the analysis. Bischoff and Dedrick assumed an instantaneous equilibrium between blood and tissue in each body region, with redistributions resulting from the addition of drug to the blood phase during initial dosing and the mixing of blood of different drug concentrations from the different tissue phases. In the present model, it was assumed that equilibrium conditions in each tissue phase are approached in a simple, linear manner, with characteristic times determined by tissue volumes and blood flow rates. This model distinguishes between equilibrium drug concentrations in tissue phases and the volumes of blood associated with each phase.

The model was initially evaluated using methohexital as the prototype of other intravenous drugs to be considered for future analysis. The behavior of the model after intravenous injection is as follows. At time zero, the drug is wholly absorbed in the blood. Thereafter, rapid redistribution occurs in which most drug is dissolved by lipid cells, although a substantial amount becomes bound to visceral protein rather quickly. As the blood concentration decreases, reabsorption of drug from the visceral tissue is fairly rapid. The large amount of drug dissolved in adipose tissue is reabsorbed by the blood at a much slower rate and gradually removed from the blood by liver metabolism.

For the case treating the faster effective flow rate to adipose tissue ($Q_p = Q_l$), the effects of lipid solubility are more pronounced: blood concentration decreases more rapidly, visceral concentration does not reach as high a level, and the total amount of drug absorbed by lipid cells is much greater. According to the model, neither the concentration nor the total amount of drug in the lean tissue is ever very large. This condition results from the characteristic time for reaching equilibrium in lean tissue, V_l/Q_l, being relatively long (0.5 hr), so the blood flowing through the tissue has a very low drug concentration by that time. The same situation would occur in the visceral tissue were it not for the very short characteristic time, V_s/Q_s (1.5 min) for this tissue phase to equilibrate with the blood; at that time the blood is still fairly high in drug concentration.

The appropriateness of the model to describe the distribution of other intravenous drugs was tested by calculating the distribution kinetics of thiopental, using the values of the physicochemical parameters known for this drug. Two values of thiopental differed markedly from methohexital: the fraction of unbound drug ionized at pH 7.4 and the lipid solubility coefficient, K_p. The former value was 0.39 for thiopental compared to 0.24 for methohexital, and the latter value was 89 for thiopental and 65 for methohexital. These values for thiopental, along with the slightly different values for the unbound fraction of thiopental in plasma and protein binding site association constants, significantly influenced the calculated values of thiopental distribution. The results for thiopental showed a more rapid decrease in blood concentration, a higher concentration in adipose tissue, and a lower peak concentration in visceral tissue compared to methohexital for the same intravenous dose. These data support the suggestion by Brand *et al.* (18) that the greater potency and more rapid recovery from methohexital compared to thiopental were due to its slower decrease in blood levels and smaller accumulation in fat, allowing for more distribution to the brain tissue and subsequent faster elimination from the body.

By assuming K_r (the reaction rate constant describing what fraction of available drug passing through the liver is metabolized) to have a value of unity, the rate of liver metabolism was essentially a function of the changes in blood concentrations of the nonionized unbound drug fraction. Thus, the parametric changes for thiopental were expected to influence its calculated rate of metabolism. In fact, the calculated rates of thiopental and methohexital (14 and 20% of the administered dose, respectively, during the 1st hr) agreed favorably with experimental values (15 and 15–19%, respectively) reported by Brand *et al.* (18), a result providing confidence in the predictable nature of the model.

Obesity was selected as the physiological alteration for stressing the model because of the existence of accurate methods for obtaining values for this parameter in future studies (23, 24). In an obese subject of twice normal weight and volume, where the added volume was assumed to be all adipose tissue, the peak value of drug concentration in visceral tissue was the same after a 140-mg dose as that in the normal subject. If it is assumed that the visceral drug concentration reflects the same proportional brain concentration in both cases, the results indicate that an obese subject needs no additional increase in dose to provide similar brain levels. Thus, if the intravenous dose were based on the weight of the subject, more drug would be predicted to distribute in the viscera and, therefore, brain tissue.

This prediction was verified when the peak concentration of viscera of the obese subject was calculated to be twice that of the normal subject after 2 mg/kg iv. This observation is consistent with the fact that clinical induction doses of intravenous anesthetics are not derived on the basis of patient body weight but remain as established narrow dose ranges derived from the amounts of drug observed to produce clinical anesthesia.

The nonlinear pharmacokinetic model of intravenous anesthesia presented here seems capable of semiquantitative prediction of drug concentrations for times longer than about 1 min, using literature values for all parameters except the liver reaction rate constant. The two cases, $Q_p = 0.26$ and $Q_p = Q_l$, seem to provide lower and upper bounds, respectively, on the actual effective rate of drug delivery to adipose tissue within the framework of the present calculations. The strong points of this model are the simple ramp functions (Fig. 1) that provide an approximate description of the approach to equilibrium conditions in each tissue phase. The weak points are the oversimplifications incorporated in the simple ramp functions and the assumption of a single homogeneous phase to describe all of the blood throughout the body.

An improved model could easily be formulated by adding the gradual approach to equilibrium concept to the kinetics given by Bischoff and Dedrick (9) or to their more sophisticated, later analysis (10). However, it seems more reasonable at this stage to abandon the static law of mass action and to apply the elementary reaction rate theory to develop an improved model much in the spirit of Wagner (22).

Because the only easily controlled experimental variable besides total dosage is the rate at which the drug is administered, it is obviously important to develop an improved model in which the drug distribution at times less than 1 min can be adequately treated. Such a model can be studied and improved experimentally to develop values for its parameters that fit various actual situations. When this has been accomplished, one might justifiably assign some predictive capability to the model.

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CSTRIP, a Fortran IV Computer Program for Obtaining Initial Polyexponential Parameter Estimates

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Abstract □ A new exponential stripping program, CSTRIP, has been developed. This program overcomes the problems associated with the use of previously published techniques and enables the rapid economical calculation of initial polyexponential parameter estimates. Values for the coefficients and exponents of the exponential terms are calculated as well as estimates of lag times. An exhaustive search procedure ensures that the results are comparable to, or better than, those obtained by manual residual methods.

Keyphrases □ Pharmacokinetic modeling—calculation of initial polyexponential parameter estimates by a Fortran computer program □ Polyexponential parameter estimates—pharmacokinetic modeling, calculation by a Fortran computer program □ Computer programs, Fortran—calculation of initial polyexponential estimates for use in pharmacokinetic modeling □ Automated computer analysis—initial polyexponential parameter estimates for use in pharmacokinetic modeling, Fortran program

Pharmacokinetic models have proven to be a succinct method of describing the behavior of drugs *in vivo*. Classical linear pharmacokinetic models are represented by systems of homogeneous linear differential equations with constant coefficients. Solutions of such systems are given by the sums of exponential terms. Calculation of the numerical values of the exponents and coefficients of the exponential terms is often laborious and time consuming. Fortunately, the operations involved in exponential stripping are generally systematic and lend themselves to computer programming and solution by machine.

Theoretical approaches to exponential stripping have been discussed (1–7). However, many procedures are difficult to adapt to automated computer analysis.

One technique (1) employed a modification of the standard residual method, where the concentration of drug, C, was plotted against its first derivative, $-\Delta C/\Delta t$. This procedure yielded more erratic results than conventional residual methods because of the extreme sensitivity of the derivative to experimental error. Other techniques (2, 3), based on the theory of difference equations, proved to be impractical due to computational difficulties; unreliable solutions were obtained in the presence of small experimental errors. These methods also required equally spaced time intervals and only resolved the sums of exponentials having *positive* coefficients. Implementation of other approaches (4, 5) was prevented by similar considerations.

A computer algorithm (7), based on the residual method, was reported to be suitable for fully automated data analysis. This procedure had the following desirable characteristics: (*a*) sums of exponentials having positive and/or negative coefficients were accurately analyzed, and numerical values of coefficients and exponents were computed; and (*b*) unequally spaced data were acceptable, and no numerical instability arose during computation. However, this program required a minimum of three points for each exponential, and its use gave results that were not in good agreement with