Keyphrases

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Shortcomings in Pharmacokinetic Analysis by Conceiving the Body to Exhibit Properties of a Single Compartment

By S. RIEGELMAN, J. C. K. LOO, and M. ROWLAND

In the past, pharmacokinetic assessment of drug absorption, metabolism, and excretion usually have been based on the concept of the body behaving as a single compartment. After rapid i.v. injection, provided that blood samples are taken sufficiently soon after injection, at least a bi-exponential curve is obtained. The initial portion of this curve, the so-called rapid distribution phase, has been ignored without proof, and it has been assumed that the single-compartment concept does not introduce large errors into the subsequent calculations. On the basis of first principles, at least one additional peripheral compartment must exist for virtually any compound introduced into the body. Such a model is physiologically compatible with distribution of the drug throughout the body under perfusion and diffusion forces. The two-compartmental open-system model is discussed in respect to the error introduced into the usual absorption rate and elimination rate calculations and on the estimation of the volume of distribution of various drugs.

PHARMACOKINETIC STUDIES are usually undertaken to attempt to define, as accurately as possible, the rates of absorption, metabolism, and excretion of a drug and its metabolites. The analyses of data, obtained after administration of a drug to man or animals, have most commonly been based on the presumption that it is adequate to consider the body as exhibiting the properties of a single compartment. Since a model is only conceived to serve the purposes of the scientist, it need not be any more complex (nor should it be any less simplified) than required to serve this function. However, it is scientifically unsound to continue to accept a model because it is often used; instead it should be questioned until there is sufficient evidence to support its adequacy for the purposes for which it was designed. Surprisingly, within the knowledge of the authors, there appears to have been no critical tests of the validity of the single-compartmental model. This paper is the first of a series which will attempt to examine this model and point to some of the limitations and incorrect reasoning that it imposes on these analyses.

It is the purpose of this paper to emphasize that a central and at least one peripheral compartment appear essential to describe adequately the distribution of the drug in the body. Not only is such a model sufficiently realistic when viewed on a physiological basis, but it is mathematically more acceptable than the one-compartmental model.

DISCUSSION

Physiological Aspects of the Mammillary Model—Compounds are distributed throughout the body by the blood and vascular network acting as a carrier system. One conceives of a model which represents drug distribution and elimination to be made up of a central compartment with interchanging connections with one or more peripheral compartments. Such a model has been called a mammillary model (1). While blood is a major

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essential component of the central compartment, it will be made clear later that the compartment is larger than the plasma volume. When a drug is injected rapidly into a vein, it initially mixes with a small volume of plasma forming a bolus. However, as it passes through various capillary beds, filtration and diffusion forces cause some of the molecules to transfer into the surrounding tissues. These events take place extremely rapidly (2), so that even during the first few moments while the drug solution becomes physically mixed with the plasma, the solute has already penetrated into a much larger volume.

The rate of uptake of a compound into the tissues is controlled by several forces, including the rate of flow of blood through the tissue, the mass (volume) of the tissue, and the partition characteristics of the compound between the plasma and the tissue. The interrelationship of these factors is defined by Fick's law of perfusion and has been discussed in detail by Kety (3) and others (4, 5). The rate of flow of blood through the tissues varies in each tissue from highs of 500 ml. to less than 2 ml. of blood/100 ml. of tissue/min. The partition coefficient of the compound into the various tissues also is affected by many factors, such as its relative lipoid solubility, pH, and complexation with proteins, nucleic acids, *etc.* It is clear from the above that drugs will distribute into tissues in a highly complex manner and in a real sense will exhibit different concentrations down to the subcellular level. This almost infinite degree of complexity brings confusion into the issue of multiple-compartmental analysis merely because we are so anxious to place physiological meanings to the compartments defined by a particular experiment.

The distribution of a drug into various tissues as described above is spoken of in anesthesia and physiological literature (5, 6) as the perfusion-limited, multiple-compartmental model. If the body must be divided into N-compartments, there should be $N - 1$ exponential terms in the resultant equation.[1] The fact that it is rarely possible to determine more than two or three exponential terms in these studies indicates that many of the tissue compartments exhibit sufficient similar properties to pool into large groups or are too small to be detected. The anesthesiologist–physiologist conceives of the body as dividing into four groups according to their perfusion and partition characteristics.

A highly perfused lean tissue group, consisting of the heart, lung, hepatoportal system, kidneys, endocrine glands, and under certain instances the brain and spinal system.

A poorly perfused lean tissue group, consisting of the large mass of muscle and skin tissue.

A fat group, consisting of the adipose tissue, including marrow.

A negligible perfusion tissue group, consisting of bone (not marrow), teeth, ligaments, tendons, cartilage, contents of the alimentary canal, and hair. This final group can usually be ignored in pharmacokinetic analysis except in those cases when considering drugs (tetracyclines) or elements (calcium, phosphate) which concentrate in this compartment.

Recently, Perl and co-workers have shown (7) that the multiple-compartmental model based on distribution of the compound solely by a perfusion-limited process is unrealistic, at least as it applies to fat-soluble compounds (8). Even though fat is estimated to have approximately the same perfusion rate as muscle tissue, many compounds are much more soluble in the fat than in other tissue masses. Therefore, direct diffusion between the fat pads and the adjacent tissues becomes a significant pathway due to the gradient in concentration which develops as the neighboring tissues "fill up" at unequal rates from the common source, the arterial blood. Perl and co-workers propose that the adipose tissue should be considered to be stored into two types of depots. In one (subcutaneous, interstitial, *etc.*), the adipose tissue has a boundary surface in contact with the more slowly perfused lean tissues, such as the resting muscle and skin. In the other, the adipose tissue (omental, perirenal, *etc.*) has a boundary surface in contact with the highly perfused lean tissue. Strong evidence to support this contention was presented from studies on the simultaneous uptake of nitrous oxide and cyclopropane in man at subanesthetic levels. These compounds have identical partition characteristics into body fluids and tissues, except that cyclopropane is eight times more soluble in fat than is nitrous oxide. An approximately constant 5% difference in the alveolar concentration of the two gases was obtained when they were simultaneously administered. This was larger and more rapidly evolved than could be explained on any physiologically acceptable modification of the simple perfusion-limited, multicompartmental model. The magnitude and rate of onset of the concentration difference could only be adequately explained on the basis of diffusional forces modifying the perfusion-limited distribution and causing the cyclopropane to enter more rapidly the two separate fat compartments *via* the neighboring tissues.

From the above discussions it seems likely that one would not have to consider the body to be so highly compartmentalized as was originally thought. In effect, the two fat compartments surrounded by tissues of different perfusion characteristics simply modify the effective volume of these two tissue groups and their rate of equilibration at least insofar as the pharmacokinetic calculations are concerned. Therefore, since the uptake of the drug by the highly perfused tissue group is usually so rapid, it can be conceived mathematically to be part of the central compartment. Also, expanding the volume of the central compartment to include some extracellular fluids and the highly perfused tissue mass as well appears to be physiologically acceptable and mathematically logical.

Simultaneous to distributing throughout the body, virtually all drugs undergo metabolism. The effect of metabolism is superimposed on the distribution from the very instant the drug enters the tissues and the magnitude of its influence on the observed rate constants for the loss of the compound from the body varies from compound to compound. This effect will be discussed in detail below. The major site for metabolism, liver, as well as the minor sites, the kidneys and gastrointestinal tissues, are all included in the central compartment in the presently conceived model. This will simplify many mathematical considerations (9). From the viewpoint of what can be detected from the blood,

[1] The so-called two-compartmental open-system model in an exact sense has at least one additional compartment, the urine, feces, or metabolite.

it is, therefore, physiologically acceptable to conceive of a bi- or tri-exponential function representing body distribution of the drug from a central into one or two peripheral compartments, with metabolism and excretion taking place from the central compartment. This viewpoint in itself does not prove that a two- or three-compartmental model is better than the one-compartmental model, or that a more complex model may not be needed to meet the known physiological or pharmacological facts. The intent of the above discussion is to emphasize that a two-compartmental model may be all that is necessary to achieve the declared goals of accurate assessment of the rates of absorption, metabolism, and excretion. A possible method of establishing valid experimental support for a given model can be made through studies of absorption which will be presented later.

Mathematical Basis for Reducing N-Compartmental System into a Two-Compartmental Model—From a purely pragmatic point of view, the above simplification of complex physiological phenomena needs no further justification. Yet Sharney, Wasserman, and co-workers (10) have shown that under certain precise conditions a system consisting of an arbitrarily large number of interchanging pools can be represented exactly by a two-pool or three-pool model. These authors made no *a priori* assumptions about the relative sizes of the peripheral pools and, therefore, such mammillary systems may include very small as well as very large peripheral compartments. They emphasized that such a representation of complex mammillary systems by a simple two- or three-pool model is a perfectly valid and rigorous procedure. Because no individual compartment is detected, the corresponding rate constants out of the peripheral compartments are defined by Sharney to be equal since they are not specific in any sense nor do they apply to any real tissue compartment (10). They are, however, essential to the authors' model in that they define the disposition of the drug into the rest of the body. Without their definition, the absorption and probably the metabolism and excretion characteristics of the drug are not accurately definable.

Estimation of Tissue Compartment on Basis of Material Balance—One might suggest that a peripheral compartment is detectable only in the early phases of the time course of the drug in the body and that the body takes on the characteristics of a single-compartmental model when the blood data appear to indicate monoexponential decay. The loss of the drug from the body is then specified to be the elimination rate constant. However, without presuming any specific model for distribution of a drug after an intravenous injection, it can be shown that at least one peripheral (tissue) compartment exists *throughout* the time course of the drug in the body. Material balance requires that the following equation holds true at any time:

$$\text{dose} = V_pC_p + M + E + T \quad \text{(Eq. 1)}$$

where

V_pC_p = mass of the original dose, D, in the central compartment at any time, t, as indicated by the concentration of the drug in the plasma, C_p.

V_p = volume of the undefined central compartment.

$C_p^\circ = D/V_p$ = concentration of the drug at zero time as defined by extrapolation of the curve back to $t = 0$.

M = mass of the original drug metabolized (from central compartment) by *all* processes.

E = mass of original drug excreted (from central compartment) by all routes.

T = mass of the original dose distributed to the peripheral or so-called tissue compartment at any time.

It is further presumed that metabolism and excretion take place by first-order processes with the rate constants, k_m and k_e, respectively, *i.e.*,

$$dM/dt = k_mV_pC_p \quad \text{(Eq. 2)}$$

$$dE/dt = k_eV_pC_p \quad \text{(Eq. 3)}$$

Also, defining the sum of these two processes as the elimination rate constant, $k_{el} = k_m + k_e$, then the amount of the original dose lost by all processes of metabolism and excretion up to time, t, is obtained by integrating Eqs. 2 and 3:

$$M + E \Big|_0^t = k_{el}\, V_p \int_0^t C_p dt \quad \text{(Eq. 4)}$$

where the integral term $\int_0^t C_p dt$ is the area under the plasma concentration time curve from the time of the injection to time t. Substitution into Eq. 1 and rearranging gives:

$$T = D - k_{el}\, V_p \int_0^t C_p dt - V_pC_p \quad \text{(Eq. 5)}$$

At a sufficient time, arbitrarily defined as infinite time, for all the drug to be eliminated from the body, Eq. 4 becomes:

$$\text{dose} = M + E \Big|_0^\infty = k_{el}V_p \int_0^\infty C_p dt \quad \text{(Eq. 6)}$$

from which we can substitute for $k_{el}V_p$ in Eq. 5.

$$T = D - D\frac{\int_0^t C_p dt}{\int_0^\infty C_p dt} - V_pC_p \quad \text{(Eq. 7)}$$

Equation 7 is, therefore, a method of estimating the mass of the drug which is in the tissue compartment at any time. Dividing through by dose, results:

$$T/D = 1 - \frac{\int_0^t C_p dt}{\int_0^\infty C_p dt} - C_p/C_p^\circ \quad \text{(Eq. 8)}$$

Equation 8 is useful to describe the fate of the compound from data obtained from intravenous administration of that compound. The term C_p/C_p° is the fraction of the original dose remaining in the central compartment at any time. The term T/D is the fraction of the dose which has entered and remains in the peripheral compartment at any time. Finally, the term

$$\int_0^t C_p dt \Big/ \int_0^\infty C_p dt$$

is the fractional area term and represents the fraction of the original dose which has been lost from the

central compartment by metabolism and excretion. While both metabolism and excretion can take place from the peripheral compartments, on the basis of the present knowledge, both of these processes predominantly take place in tissues included within the central compartment. Figures 1–5 are based on calculations using Eq. 8 on selected data from compounds of interest. It is clear from these data that the size of the tissue compartment varies markedly from compound to compound, as does the instant at which the central and tissue compartments reach equilibrium ($dT/dt = 0$). However, in each of the examples illustrated the data indicate the continued existence of the tissue compartment throughout the test period.

The parallelism of the slope of the two lines is a point that creates a great deal of confusion. The fraction of the drug lost from each compartment is identical when the two compartments are in apparent distribution equilibrium. However, the two compartments are not in steady state of equilibrium throughout this period, since drug mass is exchanging between the compartments per unit time. Neither can they be lumped into a single compartment without loss of certain mathematical accuracy in the calculation of the absorption and the elimination rate constants.

Many drugs cannot be easily studied from blood specimens due to the small dose administered or at times when only a small fraction of the dose remains in the central compartment. This is particularly true of amine drugs. The value of the study of urinary excretion data was shown by the farsighted and basic studies of Nelson (16–18) and others (19, 20). It should be noted that Eq. 3 listed above intrinsically presumes constant urinary clearance. Therefore, if urinary excretion samples were taken at sufficient frequency, a similar analysis of the data could be made. This is seen in Fig. 6 where blood and urinary data on mannitol (21) are represented. Unfortunately, it is not easy to obtain sufficient urine samples for such an analysis in each case. However, analysis of urinary data for the absorption and elimination rate constants are no more valid than their counterparts calculated from the blood data; indeed, it is likely that they may be less accurate due to variations in urinary pH, flow rate, and when a small fraction of the drug is excreted intact.

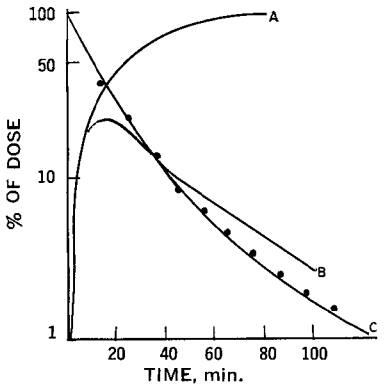


Fig. 1—Percent of dose estimated to be in the central compartment, tissue compartment, and eliminated after a 100-mg. i.v. injection of penicillin G into a male (12). Key: A, *amount eliminated;* B, *tissue compartment;* C, *central compartment.*

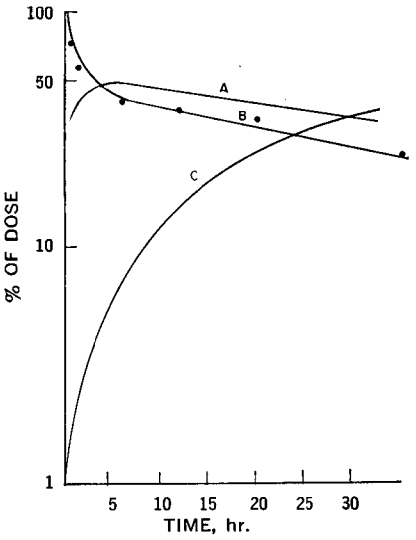
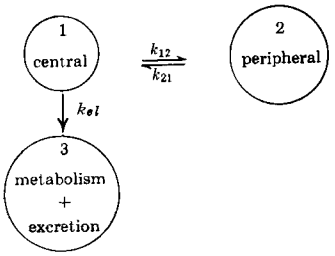


Fig. 2—Percent of dose estimated to be in the central compartment, tissue compartment, and eliminated after a 1.0-Gm. i.v. injection of pentobarbital into a male (13). Key: A, *tissue compartment;* B, *central compartment;* C, *amount eliminated.*

Two-Compartmental Open-System Model—The above discussions all lead to the inevitable conclusion that the body behaves more like a two-compartmental open system, such as is indicated in the diagram shown in Scheme I.



Scheme I

It is believed that this model was first related to drug kinetics by Teorell in 1937 (22). Since then it has been discussed in various degrees of sophistication by Dominguez (23), Sheppard (24), Solomon (25), Shore (26), Riggs (27), Mathews *et al.* (28), Nelson (29), Resigno and Segre (30), Sharney *et al.* (31), and others. Solution of the differential equations resulting from such a model yields the following integrated solution:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 9)}$$

$$C_p^\circ = A + B \qquad \text{(Eq. 10)}$$

or

$$1 = A/C_p^\circ + B/C_p^\circ = A' + B'$$

$$A' = (k_{21} - \alpha)/\beta - \alpha;\ B' = (k_{21} - \beta)/\alpha - \beta \qquad \text{(Eq. 11)}$$

$$\alpha \cdot \beta = k_{21} \cdot k_{el} \quad \text{(Eq. 12)}$$

$$\alpha + \beta = k_{12} + k_{21} + k_{el} \quad \text{(Eq. 13)}$$

$$\int_0^\infty C_p dt = A/\alpha + B/\beta = C_p^\circ/k_{el} = D/V_p k_{el} \quad \text{(Eq. 14)}$$

Therefore

$$k_{el} = 1/(A'/\alpha + B'/\beta) \quad \text{(Eq. 15)}$$

$$k_{21} = A'\beta + B'\alpha \quad \text{(Eq. 16)}$$

$$k_{12} = A'B' (\beta - \alpha)^2/k_{21} \quad \text{(Eq. 17)}$$

The best method of estimating the coefficients, A and B, and the hybrid rate constants, α and β, of Eq. 9 are not the subject of this paper except to point out that no mathematical method will substitute for sufficient blood samples taken at the critical times and accurately assayed. Several authors have discussed the analysis of these curves (32–34) and present numerical and computer solutions of the equation. Wagner and Northam recently discussed the relationship between the volume of distribution and the half-life of a compound after an i.v. injection (35) wherein they present several equations equivalent to those listed above.

Influence of Two-Compartmental Open-System Model on Estimation of Absorption Rate Constant—It should be clear from examination of Figs. 1–6 that a variable fraction of the drug molecules leave the central compartment during the distributive phase. Therefore, when the drug is not injected but is absorbed from a site, such as the gastrointestinal tract, a fraction of the absorbed molecules is distributing into the tissue compartment. This phenomenon cannot be ignored while calculating the true absorption rate.

It will be shown in a later paper (36) that calculation of the absorption rate ignoring the existence of the peripheral compartment is subject to significant errors and that an absorption rate equation including a peripheral tissue compartment term allows recovery of known rates of drug infusion into the body, while the former methods lead to incorrect estimates. These facts lend significant support to the presently conceived model. Since such calculations are essential to the basic understanding of drug absorption, their correct interpretation is not unimportant, particularly since *in vivo–in vitro* relationships have been drawn up on the basis of these types of analyses (37, 38).

Influence of the Two-Compartmental Open-System Model on Calculations of Volume of Distribution—A detailed discussion of the calculations of the volume of distribution (V_d) as it is affected by the concept of a two-compartmental open-system model has been presented by Riggs (39). The volume of distribution of a compound can only be defined when the tissue compartment is in equilibrium with the central compartment (*i.e.*, when $dT/dt = 0$) at least insofar as this model is concerned.[2] The volume of distribution is merely one of the kinetic constants of the model being tested. Within the experimental error, the same value should be obtained from the various methods of estimation. The V_d's calculated by the several biased methods

[2] This is not mathematically the unambiguous definition for the steady state of equilibrium (27), but applies in the model since it is assumed that no drug loss takes place from the tissue compartment.

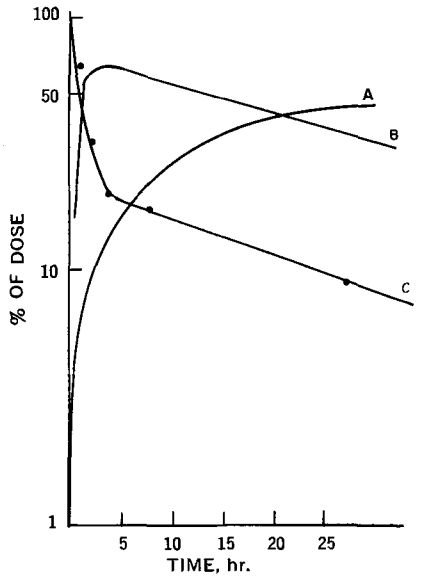


Fig. 3—Percent of dose estimated to be in the central compartment, tissue compartment, and eliminated after a 750-mg. i.v. injection of thiopentobarbital into a male (13). Key: A, amount eliminated; B, tissue compartment; C, central compartment.

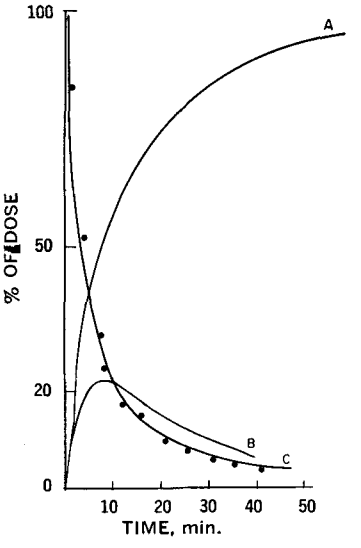


Fig. 4—Percent of dose estimated to be in the central compartment, tissue compartment, and eliminated after a 650-mg. i.v. injection of acetylsalicylic acid into a male (14). Key: A, amount eliminated; B, tissue compartment; C, central compartment.

vary considerably, when sufficient data points are taken, which they should not do if the single-compartmental model held. However, calculation of the volume constant defined by the two-compartmental open-system model presented above appears to yield a constant value independent of the method of calculation (40).

Influence of Two-Compartmental Open-System Model on Estimation of Metabolism and Excretion Rate Constants—It is clear from Eqs. 12 and 13

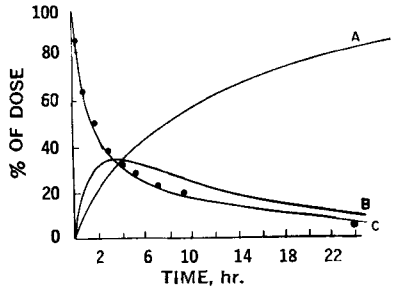


Fig. 5—Percent of dose estimated to be in the central compartment, tissue compartment, and eliminated after a 142-mg. i.v. injection of griseofulvin into a male (15). Key: A, *amount eliminated;* B, *tissue compartment;* C, *central compartment.*

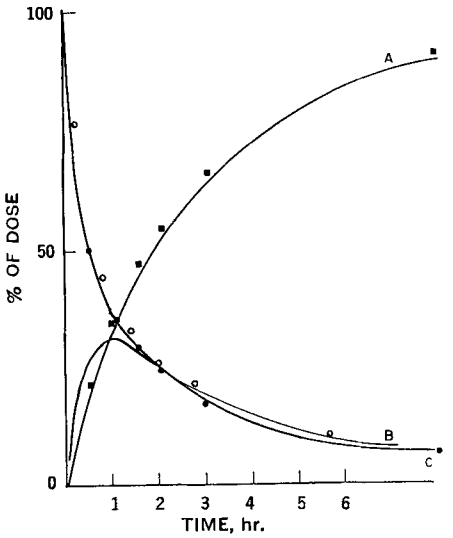


Fig. 6—Percent of dose estimated to be in the central compartment, tissue compartment, and eliminated after a 25.8-Gm. i.v. injection of mannitol into a male. Also included is a curve representing the normalized urinary excretion data (21). Data from subject: R = 3. *Curves drawn with two-compartment analog computer program. Points represent appropriate blood and urine data. Key:* A, *amount eliminated;* B, *tissue compartment;* C, *central compartment.*

that α and β are hybrid rate constants, each influenced by all of the rate constants of the system. One must be warned, therefore, that with such a multiple exponential equation, one has no right to identify a particular term with a particular process. The elimination rate constant for the process is denoted as k_{el} in the two-compartmental open-system model given above. It is incorrect to designate β, the slower rate constant of the bi-exponential, as the elimination rate constant as is the usual practice in pharmacokinetics. However, some descriptive term should be available to refer to this hybrid constant. Therefore, the term "*disposition* rate constant[3]" is proposed, attempting thereby to imply that it includes both distribution and elimination.

In order to illustrate the relation between the true elimination rate constant, k_{el} and β, Eq. 14 may be rearranged as follows:

$$k_{el} = C_p^\circ/(A/\alpha + B/\beta) \qquad \text{(Eq. 18)}$$

However, A/α is often negligible relative to the magnitude of B/β. Equation 18 may be reduced to the following approximation:

$$k_{el} \approx \left(\frac{C_p^\circ}{B}\right)\beta \qquad \text{(Eq. 19)}$$

The ratio C_p°/B varies from one drug to another, but often ranges from 1.5–2.5. However, compounds which distribute out of the central compartment into the peripheral compartment(s) to a large degree will show a much higher proportionality constant. For example, from the published data on intravenous injection of radioactive digitoxin (41), it can be estimated that k_{el} is at least 15 to 40 times larger than the slowest disposition rate constant.[4] Most amine drugs are known to distribute to a large extent into the tissues. This will result in a high ratio of C_p°/B, and therefore, the true elimination constant may be many times larger than the value of the slowest disposition rate constant. In some pharmacokinetic evaluations, this error may play a minor role, such as when one is attempting to evaluate dosage form effects. However, when urinary data are being analyzed, it is common to presume that the slowest disposition rate constant is identical with the true elimination rate constant and that the metabolic rate constant is equal to the disposition rate constant times the fraction of the drug metabolized. Such assumptions result in a large error.

When a pharmacologically related and structurally similar series of compounds are being studied, it is exceedingly important to attempt to evaluate the true elimination rate constant. Introduction of one organic substituent into a molecule may cause a significant change in the tissue distribution, as well as in the metabolism and excretion processes. It is important to discriminate among these factors to a greater extent than we have done to date if we are to better understand how substituents are influencing distribution, metabolism, and excretion characteristics.

Not only does the two-compartmental open-system model become important in the analysis of absorption, metabolism, and excretion of drug, it also markedly influences the analysis of turnover rate of normal body constituents, such as ascorbic acid (42), glucose (43), iron (44), and other compounds. The turnover rate cannot be defined by injecting a known dose and estimating the decline to the homeostatic level, presuming the drug is distributing into a single compartment. It is clear that such an analysis is based on a questionable postulate, since most of these drugs have been shown (45, 46) to require multicompartmental models to define their disposition and elimination from the body.

Relationships of Two-Compartmental Model to Consideration of Drug Interaction in Man—In recent years, it has become apparent that drug

[3] The term *dispose* is taken from the French, meaning to place apart.

[4] In this instance, a tri-exponential was observed by the author (41).

administered during or immediately before asecond compound is taken may influence the pharmacological activity of the second drug. Several different mechanisms have been proposed for these drug interactions. In one instance, the first drug is said to induce changes in the level of metabolizing enzymes. When the second drug is administered, it undergoes a more rapid rate of metabolism. A second form of drug interaction has been postulated for some drugs when given concurrently where the first drug partially displaces the second drug from protein binding sites, thereby allowing for a change in drug distribution. In other instances, the second drug may cause an increase in the excretion rate or may reduce the rate of absorption. It should be apparent that the two (or multiple) compartmental open-system model is a much more meaningful model to examine the relative effect of drug *A* on drug *B*.

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Keyphrases

Pharmacokinetics of drug absorption
Mammillary model
Compartments, consideration of body as one and two
Absorption rates—two compartmental
Drug distribution volume—two compartmental
Tissue compartment—estimation
Metabolism-excretion rates, two compartmental