Two-Compartment Pharmacokinetic Models: Computer Simulations of Their Characteristics and Clinical Consequences

FRED P. ABRAMSON

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Abstract □ Computer simulations of two-compartment models of drug disposition were made. These simulations show how variations in each of the three intercompartmental rate constants are related to altered blood and tissue concentrations. Various simulations following rapid injection or continuous infusion are presented to demonstrate the general behavior of such a pharmacokinetic model. A system of drug classification based on comparative values of a drug's intercompartmental rate constants is proposed, and characteristics and consequences of each class are discussed in terms of possible therapeutic results.

Keyphrases □ Pharmacokinetic models—two-compartment models, computer simulations of their characteristics and clinical consequences □ Models, pharmacokinetic—two-compartment models, computer simulations of their characteristics and clinical consequences □ Drug disposition—two-compartment models, computer simulations of their characteristics and clinical consequences

At least two compartments are required in pharmacokinetic modeling: one for the drug in vascular and highly perfused tissues and one for more peripheral tissues. The physiological basis for this viewpoint was stated clearly by Riegelman *et al.* (1). Most published descriptions of the two-compartment model (2–6) have a mathematical focus to solve the simultaneous differential equations for the intercompartmental rate constants. In some cases, this approach does not provide intuitive understanding of the behavior of drugs that demonstrate two-compartment pharmacokinetics.

A series of computer simulations in which each of the three intercompartmental rate constants is varied individually has been useful in understanding and predicting the behavior of two-compartment systems. Illustrations from these simulations are presented to demonstrate the use of the method; such information is not available in textbooks or in the periodical literature.

In addition, these simulations point out situations where the conventional simplification of the two-compartment model to a one-compartment approximation may present substantial errors. These errors carry over into nomograms, which are used frequently in the calculation of adjusted doses in patients with impaired excretory capability.

EXPERIMENTAL

An analog computer[1] was used for the simulations. The flow charts for the simulations are shown in Fig. 1. Conversions to logarithmic coordinates were performed manually.

The data are presented in arbitrary units. The time scaling can be converted from time units (TU) to any desired clock time by simple substitution. Some data are plotted in units of half-lives to emphasize the similar characteristics of drugs whose intercompartmental rate constants have similar proportionality.

The intercompartmental rate constants are given in Fig. 2. For simplicity, the drug in question is not metabolized. In this way, the disappearance of the drug from the body can be accounted for quantitatively by cumulative urinary excretion. Except for the amount of drug excreted into the urine, the overall behavior of any simulation is independent of the processes by which the drug is removed, as long as first-order kinetics are appropriate.

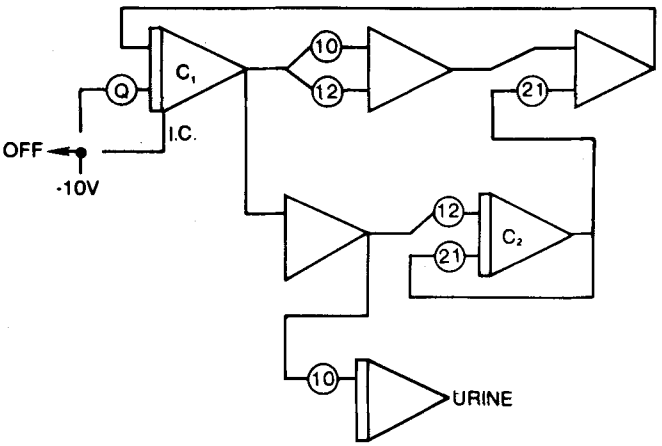

Figure 1—*Analog computer flow chart for two-compartment simulations, where C_1 and C_2 are the central (serum) and peripheral (tissue) compartment concentrations, respectively; 10, 12, and 21 refer to the intercompartmental rate constants seen in Fig. 2; Q represents the infusion rate; and I.C. is the initial condition on the amplifier representing C_1. For infusion simulations, the −10-v supply was connected through Q and turned off at an appropriate time. For simulations of intravenous dosing, the −10-v supply was attached to the initial conditions representing an instantaneous injection of drug. For one-compartment simulations, the coefficients k_{12} and k_{21} were set at zero.*

RESULTS AND DISCUSSION

The parameters of a two-compartment system are characterized best following rapid intravenous administration of a drug. Figure 3 contrasts the time course of a two-compartment system with two different one-compartment simulations and demonstrates the differences in the models.

The β value in a two-compartment model is not the same as the k_{10} value in a one-compartment model. If a change in k_{10} occurs for a subject, the resultant change in β is not necessarily proportional. The behavior of a two-compartment system cannot be approximated by using the same k_{10} in a one-compartment model. The steepest line in Fig. 3 makes that approximation, but its half-life is only about one-fourth of that of the two-compartment model. A one-compartment model having a k_{10} equal to β from the multicompartment system has the proper half-life but has several other differences.

The upward lines in Fig. 3 show the excretion into urine in a two-compartment system and in a one-compartment system with the same half-life. At approximately 16 TU, the distribution phase appears to be over. At that time, 49% of the drug has been excreted in the two-compartment system, while only 34% has appeared in urine in the analogous one-compartment simulation. The special behavior of the central compartment during the distribution phase is demonstrated in this comparison.

The central compartment concentration of drug is initially equal in both systems. Excretion is assumed to occur from the central compartment; thus, when k_{10} in a two-compartment system is 0.10 TU^{-1}, there

[1] Model 580, Electronic Associates Inc., West Long Branch, N.J.

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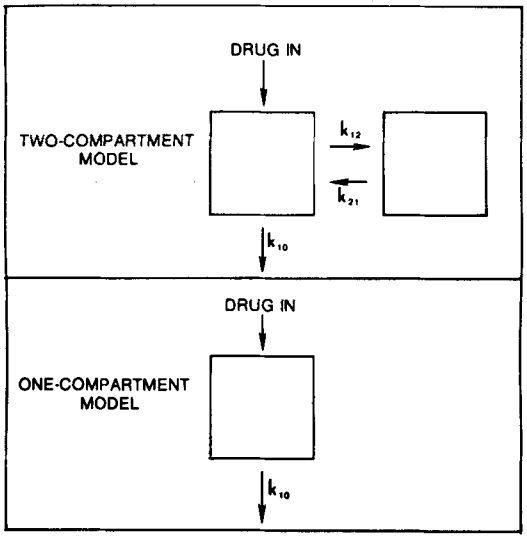

Figure 2—*Pharmacokinetic models used in simulations.*

is faster renal excretion than in the one-compartment simulation in Fig. 3. That k_{10} value is set equal to the β value (0.026 TU^{-1}) in the two-compartment system.

A high rate of drug elimination occurs during distribution, but this phase ends as sufficient drug is transferred from the central to the peripheral compartment to create an equilibrium between the two compartments. The greater the drug concentration in the peripheral compartment, the lower is the urinary excretion. Thus, in a two-compartment system, urinary excretion is initially fast but slows throughout the distribution phase. The highest concentrations of drug will reach the kidneys and the rest of the urinary tract during distribution following rapid intravenous dosing.

Another aspect of the two-compartment system is that, after distribution, drug also is contained in a tissue compartment, which may not be at the same concentration as the central compartment. In this example of a two-compartment model, the tissue concentration is 2.6 times the serum concentration. This factor is the major determinant of the smaller serum concentrations seen.

The fact that $\beta \neq k_{10}$ in a two-compartment system and the consequences with respect to drug disposition are not easily appreciated. Gibaldi and Perrier (7) demonstrated this inequality by plotting β *versus* k_{10} at several values of k_{12} and k_{21}. A very nonlinear relationship was obvious in their plot. Figure 4 shows four sets of data for serum concentrations where only the elimination rate constant was varied.

The relationship between β and k_{10} is in the form of the solution to a binomial equation also involving k_{12} and k_{21} (3). The first two columns

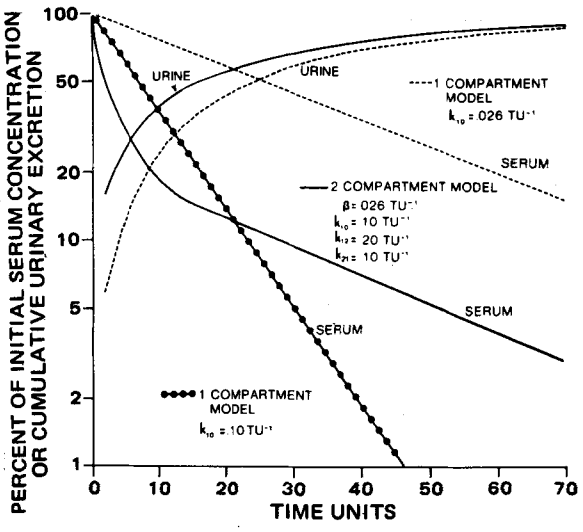

Figure 3—*Relationships between a two-compartment model and two one-compartment approximations following rapid intravenous administration.*

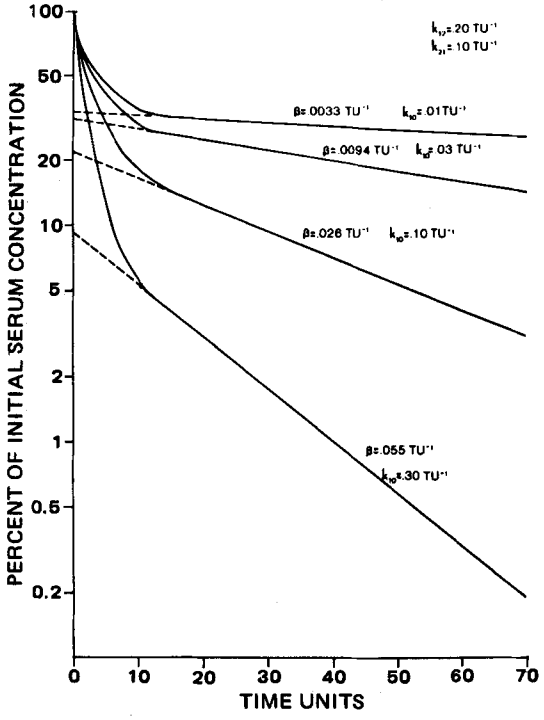

Figure 4—*Effects of variations in* k_{10} *on the behavior of a drug exhibiting two-compartment kinetics following rapid intravenous administration;* k_{12} *and* k_{21} *are constant.*

of Table I show how these two parameters behave in the two-compartment simulations shown in Fig. 4. For low values of k_{10}, β increases in a fairly linear fashion. As k_{10} increases, it no longer is the rate-limiting step in drug elimination from the body. The relationship between k_{21} and k_{12} now is more important. Thus, a tripling of k_{10} from 0.10 to 0.30 TU^{-1} gives only a doubled β. If k_{10} increased further, β would increase at a diminishing rate. However, at all values of k_{10}, k_{10} is greater than β. This phenomenon was observed by Juskō and Gibaldi (8), who analyzed kinetic data for penicillin G with and without probenecid. Although probenecid reduced k_{10} to 46% of the control value, β was reduced only to 78%, a clear example of how changes in k_{10} do not relate linearly to changes in β.

Although there is an obvious increase in the steepness of the β-phase with increasing k_{10}, there also is a strong inverse relationship between k_{10} and the serum concentration where the β-phase begins. Again, this is a consequence of increased drug elimination during the α-phase. By the time that each simulation reached its β-phase (~16 TU), the percentages of drug excreted were 8, 20, 49, and 80 for k_{10} values of 0.01, 0.03, 0.10, and 0.30, respectively. Thus, it is not appropriate to interpret a plasma decay curve with a pronounced α-phase, such as that for k_{10} = 0.30 TU^{-1}, as indicative of a large amount of drug in tissues. A large ratio between the extrapolated initial concentrations of the α-line (A_0) and β-line (B_0) may be due to extensive tissue uptake or to extensive drug elimination during the distribution phase. Drug elimination during the α-phase is responsible for errors in some techniques for assessing the volume of distribution, as will be discussed later.

Figure 5 illustrates how k_{12} affects the disposition of a drug. Here k_{10} and k_{21} are held constant. The k_{12} value of 0.20 TU^{-1} is used again, and simulations with a larger and a smaller value also are included. Clearly, k_{12} has a profound effect.

When k_{12} is high, the probability increases that a drug molecule in the central compartment will enter the peripheral compartment rather than be eliminated. If increasing quantities of drug are transferred to a peripheral compartment, they will be unavailable for elimination. The overall result will be a prolonged elimination half-life. As shown in Fig. 5, when k_{12} = 0.60 TU^{-1}, there is a rapid and extensive α-phase. In contrast to the data shown in Fig. 4, this α-phase represents mostly tissue distribution. When k_{12} = 0.06 TU^{-1}, the rate of transfer to the peripheral compartment is less important and the data appear to lie closer to a single straight line, *i.e.*, more like a one-compartment model.

Similar manipulations of k_{21} are seen in Fig. 6. When k_{21} is rapid, the simulated serum concentrations resemble the case in Fig. 5, where k_{12} was slow. In both situations, the amount of drug in the peripheral compartment is small and has little influence on the kinetics of the drug. In

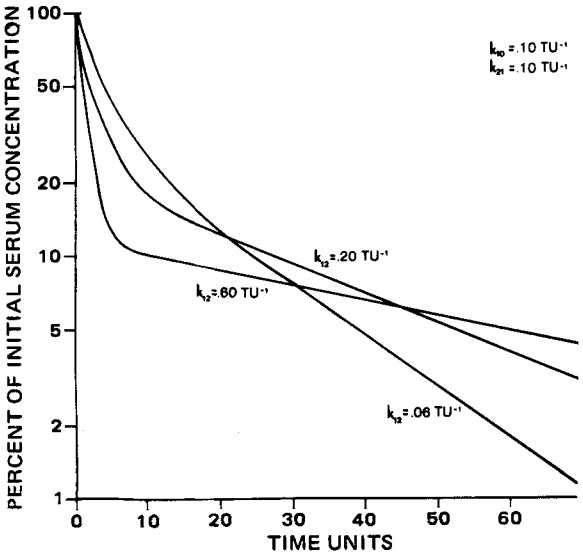

Figure 5—*Effects of variations in* k_{12} *on the behavior of a drug exhibiting two-compartment kinetics following rapid intravenous administration;* k_{10} *and* k_{21} *are constant. When* k_{12} *equals 0.60, 0.20, and 0.06* TU^{-1}, β *equals 0.013, 0.026, and 0.047* TU^{-1}, *respectively.*

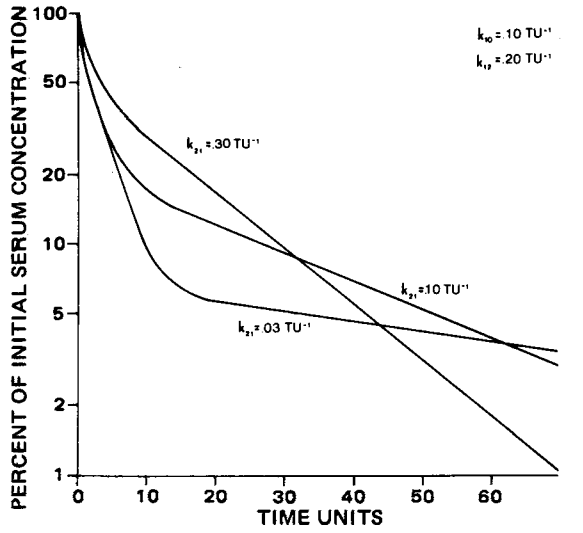

Figure 6—*Effects of variations in* k_{21} *on the behavior of a drug exhibiting two-compartment kinetics following rapid intravenous administration;* k_{10} *and* k_{21} *are constant. When* k_{21} *equals 0.3, 0.1, and 0.03* TU^{-1}, β *equals 0.055, 0.026, and 0.0094* TU^{-1}, *respectively.*

this case, the drug that moved into the peripheral compartment with a rate of $k_{12}C_1$ is returned to the central compartment by the elevated rate of return, $k_{21}C_2$. This keeps the peripheral compartment from being rate limiting. In the other simulation, where $k_{21} = 0.03$ TU^{-1}, the peripheral compartment again is important. The overall rate of elimination, $\beta = 0.0094$ TU^{-1}, is greatly reduced because the drug is only slowly returned to the central compartment for elimination.

From an overall point of view, these three first-order reactions, elimination, central to peripheral transfer, and peripheral to central transfer, are seen to compete with one another in a probabilistic way. A drug molecule in the central compartment has two fates, elimination or transfer to the peripheral compartment. The rate constants for those two processes are the probabilities of their occurrence. If k_{10} is three times greater than k_{12}, the drug has a 75% chance of being eliminated and a 25% chance of being transferred to the peripheral compartment. Once in the peripheral compartment, the drug returns to the central compartment at a rate governed by k_{21}, where again it is subject to the probabilities of excretion or transfer as described previously. Thus, the effect of each intercompartmental rate constant is buffered by the values of the other parameters. When all of the constants are of comparable magnitude, there will be a less than linear effect on a drug's overall kinetics for any change in a specific rate constant.

These computer simulations also permit evaluations of various ways of calculating the volume of distribution. In the computer, the actual volumes of each compartment are fixed and known. As a pharmacokinetic parameter, the volume of distribution is simply a mathematical construction to explain the relationship between the absorbed dose and the resulting blood concentration. The data in Fig. 4 can be used to examine some methods for calculating volumes of distribution. The calculation in the extrapolation method is:

$$V_d = \text{dose}/B_0 \qquad \text{(Eq. 1)}$$

while that in a two-compartment model (3) is:

$$V_{d2} = V_c[1 + k_{12}/(k_{21} - \beta)] \qquad \text{(Eq. 2)}$$

Table I—Comparison of Volume of Distribution Calculations as a Function of Elimination Rate Constant

k_{10}	β[a], TU^{-1}	$V_{d,ext}$[b], arbitrary volume units	V_{d2}[b], arbitrary volume units	f_c^*
0.01	0.0033	3.0	3.1	0.33
0.03	0.0094	3.2	3.2	0.31
0.10	0.026	4.5	3.7	0.27
0.30	0.055	10.9	5.4	0.18

[a] $k_{12} = 0.20$ TU^{-1} and $k_{21} = 0.10$ TU^{-1}. [b] Assuming a dose of 100 units and an initial concentration of 100 units/volume. Therefore, the volume of the central compartment is one volume.

Table I gives this comparison. The two-compartment equation takes into account the excess excretion during the α-phase and correctly calculates a volume of distribution in the sense of describing the blood concentration that results from the actual amount of drug in the body. The anatomical volume of distribution is given by $V_d = V_c(1 + k_{12}/k_{21})$. Although this V_d value is not a correct one to relate to observed blood concentrations except following steady-state infusions, it does describe correctly the actual volume in which the drug is distributed.

The $k_{21}/(k_{12} + k_{21})$ ratio defines the fraction of the drug in the central compartment (f_c) if a steady relationship is achieved between these two compartments during infusion. Because $k_{12} = 0.20$ and $k_{21} = 0.10$, $f_c = 0.10/0.30 = 0.33$ in this case. Following an intravenous bolus, the dynamic conditions lead to (2):

$$f_c^* = (k_{21} - \beta)/(k_{12} + k_{21} - \beta) \qquad \text{(Eq. 3)}$$

These data also are included in Table I. The slower the elimination phase is, the closer the dynamic f_c^* approaches the static value of 0.33. In other words, there is no constant relationship between the blood concentration of a drug and its concentration in peripheral tissue. This may be important in relating blood drug concentrations to the pharmacological actions of a drug that acts in the peripheral compartment. For a drug exhibiting the characteristics of the fourth example in Table I (*i.e.*, a large k_{10} relative to k_{12} and k_{21}), the difference in the ratio of the tissue and blood concentrations between a rapid intravenous injection and a steady-state

Table II—Intercompartmental Rate Constants for Representative Drugs

	k_{10}	k_{12}	k_{21}
Class A: all constants nearly equal			
Lidocaine (9)	0.022 min^{-1}	0.041 min^{-1}	0.029 min^{-1}
Oxacillin (10)	0.057 min^{-1}	0.037 min^{-1}	0.060 min^{-1}
α-Methyldopa (11)	0.014 min^{-1}	0.012 min^{-1}	0.017 min^{-1}
5-Fluorouracil (12)	0.18 min^{-1}	0.20 min^{-1}	0.20 min^{-1}
Class B: k_{12} more than twice k_{10} or k_{21}			
Diazepam (4)	0.225 hr^{-1}	2.29 hr^{-1}	0.85 hr^{-1}
Digoxin (13)	0.145 hr^{-1}	0.85 hr^{-1}	0.114 hr^{-1}
Morphine (14)	0.100 min^{-1}	0.600 min^{-1}	0.045 min^{-1}
Propranolol (15)	1.5 hr^{-1}	5.9 hr^{-1}	1.3 hr^{-1}
Doxorubicin (adriamycin) (16)	0.48 hr^{-1}	5.1 hr^{-1}	0.29 hr^{-1}
Class C: k_{10} more than twice k_{12} or k_{21}			
Ampicillin (17)	1.71 hr^{-1}	0.40 hr^{-1}	0.73 hr^{-1}
Cytosine arabinoside (18)	0.33 min^{-1}	0.093 min^{-1}	0.075 min^{-1}
Cephapirin (19)	4.2 hr^{-1}	1.09 hr^{-1}	1.28 hr^{-1}
Class D: k_{10} less than half k_{12} or k_{21}			
Cyclophosphamide (20)	0.29 hr^{-1}	4.5 hr^{-1}	2.9 hr^{-1}
Theophylline (21)	0.31 hr^{-1}	2.7 hr^{-1}	3.1 hr^{-1}
Warfarin (5)	0.033 hr^{-1}	1.61 hr^{-1}	1.52 hr^{-1}
d-Tubocurarine (22)	0.017 min^{-1}	0.039 min^{-1}	0.046 min^{-1}

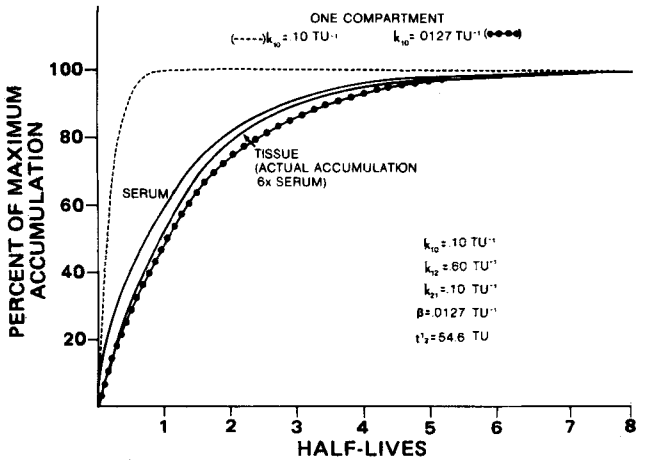

Figure 7—*Simulation of an intravenous infusion of a drug with a large* k_{12} *compared to* k_{10} *or* k_{21}. *Solid lines are from the two-compartment model. The dotted and dashed lines are two different one-compartment approximations. In the two-compartment data, the actual tissue concentration would be six times greater than the serum concentration at steady state.*

infusion is almost a factor of two. These observations are comparable to those published previously (8).

The concepts of these simulations may be applied by examining the intercompartmental rate constants of some representative drugs. Seventeen drugs were assigned to four classes in Table II. These data and the classification of each drug should be taken only as examples because data of this type vary greatly among individuals. The four classes represent conceptually different cases where particular parts of a two-compartment system play roles of greater or lesser importance.

Class A drugs have similar values for all three intercompartmental rate constants. The two-compartment simulation seen in Fig. 3 has such a relationship between its three rate constants as, for example, does lidocaine.

Certain drugs are known to accumulate extensively in tissues, as would be evidenced by a large k_{12} compared to k_{10} or k_{21}. Class B includes these drugs. For example, propranolol has kinetics similar to the $k_{12} = 0.60$ TU^{-1} curve in Fig. 5. Class C drugs have rapid elimination rate constants compared to their intercompartmental rate constants. Ampicillin is such a drug. The lowest curve in Fig. 4 is the closest simulation to this behavior. Finally, Class D drugs, such as cyclophosphamide, have relatively low excretion rate constants. The top curve in Fig. 4 typifies a Class D drug. In this situation, as was seen in Table I, there will be a linear relationship between changes in k_{10} and changes in β. There are few drugs characterized by a low k_{21}, as would result from slow release from tissues. This situation is more characteristic of drugs exhibiting a third compartment.

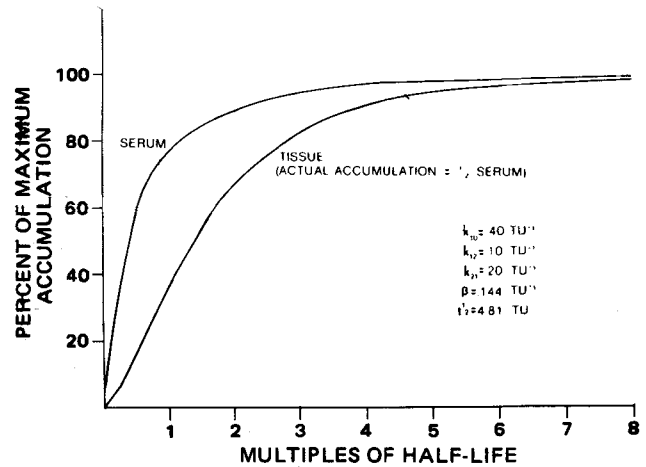

Figure 8—*Simulation of an intravenous infusion of a drug with a large* k_{10} *compared to* k_{12} *or* k_{21}. *The actual concentration of drug at steady state in the tissue compartment would be half of that in the serum compartment.*

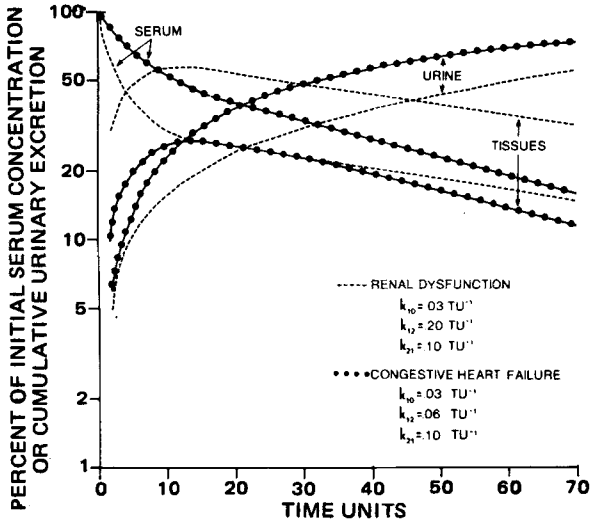

Figure 9—*Effects of two different disease conditions, each of which produces an equal reduction of renal drug clearance, following a rapid intravenous dose. The dashed lines represent simple renal dysfunction, and only* k_{10} *is reduced from the values shown in Fig. 3. The dotted lines simulate circulatory dysfunction, which also reduced tissue perfusion.*

Although all pharmacokinetic models behave as if they were simple one-compartment systems when at steady state, as would result from a constant intravenous infusion, these classes of drugs differ in their rate of approach to equilibrium after the infusion begins. For a Class B drug, Fig. 7 shows that, despite the large amount of drug accumulation in tissue, the transfer is rapid enough that there is little difference in the rate of approach to equilibrium between the central and peripheral compartments. If one compartment is assumed using a k_{10} the same as β for the two-compartment model, the approach to equilibrium is only somewhat more rapid. However, large errors would result from assuming a one-compartment model where the overall rate of elimination was k_{10}, as in the top curve.

In contrast to Class B drugs, Class C drugs demonstrate what may be therapeutically important differences between the rate of accumulation in the central and peripheral compartments. Figure 8 simulates a situation where k_{10} is large compared to k_{12} and k_{21}. The serum reaches 90% of its steady state in two half-lives, while the peripheral tissue requires four half-lives to achieve an equivalent fraction of its ultimate steady-state value. Obviously, if a Class C drug had its site of action in a peripheral compartment, a much longer infusion would be needed than would be apparent from its blood kinetics.

The effects of disease states on drug disposition also have been simulated. Starting with the set of rate constants used in Fig. 3, two disease states were examined: impaired renal function and congestive heart failure. Figure 9 shows the serum and peripheral tissue concentrations as well as cumulative urinary excretion. For renal disease, the elimination rate constant was reduced from 0.10 to 0.03 TU^{-1}. A similar decrease in renal function was used in the congestive heart failure simulation along with an equally reduced rate of central to peripheral drug transfer: k_{12} is now 0.06 TU^{-1}. This simulation is admittedly speculative because there are no intercompartmental rate constants in the literature that compare drug disposition in congestive heart failure and control conditions following rapid intravenous administration. The question is to what extent the peripheral to central compartment transfer is affected by congestive heart failure. This simulation assumes that this passive diffusion process will be unaltered.

Figure 9 shows that, although renal function is equally impaired, drug disposition in congestive heart failure differs markedly from renal disease not involving poor cardiac function. The reduced tissue perfusion in congestive heart failure leads to higher central compartment concentrations and more rapid urinary excretion. This simulation is for a Class A drug such as lidocaine. Thomson *et al.* (23) studied lidocaine in patients with congestive heart failure and found elevated blood concentrations compared to controls. Their data also show a reduced rate of drug elimination in both a rapidly perfused tissue compartment (β) and a deeper tissue compartment (γ). The present simulation also shows slower elimination in congestive heart failure ($\beta = 0.017$ TU^{-1}) than in control conditions ($\beta = 0.026$ TU^{-1}) but faster elimination than is seen in the

Table III—Ampicillin Body Elimination Rate Constants in Renal Impairment Using either a One- or Two-Compartment Model

Percent of Renal Clearance	Impaired and Normal Ratio of Rate Constants	
	One-Compartment Model[a]	Two-Compartment Model[b]
100	1.000	1.00
80	0.825	0.925
60	0.660	0.818
40	0.475	0.662
20	0.300	0.436
0	0.125	0.125

[a] One-compartment calculations use $k_e = k_{nr} + (Cl'_{cr}/Cl_{cr})k_r$ (modified from Ref. 25). [b] Two-compartment calculations use $k'_{10} = k_{10nr} + (Cl'_{cr}/Cl_{cr})k_{10r}$. $\beta = [k'_{10} + k_{12} + k_{21} - \sqrt{(k'_{10} + k_{12} + k_{21})^2 - 4k'_{10}k_{21}}]/2$.

renal dysfunction simulation ($\beta = 0.0094$ TU^{-1}). The latter difference results from the greater amount of the drug in the central compartment in congestive heart failure that is available for elimination.

THERAPEUTIC IMPLICATIONS

Except for certain highly protein-bound molecules that are confined to the vasculature, such as radiopaque dyes, any drug will distribute to some peripheral tissue compartment. Thus, a two-compartment model is the simplest description of drug behavior. Whether any particular drug in any particular patient can be described suitably by a one-compartment approach is determined only by the relationships among the three intercompartmental micro rate constants. The following discussion examines some one-compartment pharmacokinetic calculations in comparison to more accurate two-compartment situations.

There are many treatments of drug dosing in renal failure (24–27). All use only one-compartment kinetics and base their adjustment of drug dosage on some measure of renal function such as decreased creatinine clearance. Because creatinine clearance measurements take place at steady state, they are truly proportional to k_{10}. According to the literature methods, the reduction in renal function is converted linearly into a revised elimination rate constant for the drug. The only variables are the relative importance of renal function for that drug and the extent of renal impairment. This practice is acceptable when β and k_{10} vary together in a linear fashion. As was illustrated earlier in general terms, this does not hold for all drugs.

Dettli (25) presented data showing that, for ampicillin, k_n (which is β, the body elimination rate constant in normal individuals) is eight times larger than k_{nr} (which is β in patients with no renal function). From the micro rate constants in Table II for ampicillin, β is calculated to be 0.544 hr^{-1}. One would expect a patient with no functioning kidneys to have β equal to one-eighth of the normal value, or 0.068 hr^{-1}. To produce this β, k_{10nr} must be reduced to 0.11 hr^{-1}. The micro rate constant for renal excretion, $k_{10r} = 1.60$ hr^{-1}, is found by subtracting k_{10nr} from the normal $k_{10} = 1.71$ hr^{-1}.

Let k'_{10} be the elimination micro rate constant in a subject with impaired renal excretion. This k'_{10} can be used with the normal k_{12} and k_{21} to calculate β. The equation that relates k'_{10} to renal function is:

$$k'_{10} = k_{10nr} + (Cl'_{cr}/Cl_{cr})k_{10r} \qquad \text{(Eq. 4)}$$

where Cl'_{cr} and Cl_{cr} are the observed and normal creatinine clearances in the subject. A comparison of the body elimination rate constants for ampicillin using the one- or two-compartment method of calculation as a function of renal impairment is made in Table III. At both extremes of renal function, the methods agree. However, at intermediate degrees of renal impairment, the linear one-compartment calculation overestimates the reduction in body elimination compared to the more rigorous two-compartment model. The errors in the rate constants are translated directly into errors in dosing. With 20% renal function, the one-compartment calculation will lead to only 69% of the dose allowable from the two-compartment model.

As a Class C drug, ampicillin typifies the errors inherent in a one-compartment calculation for this group. Whenever k_{10} is not the rate-limiting step, there will not be a linear relationship between k_{10} and β. At the opposite end of the spectrum, the Class D drugs have an overall pharmacokinetic behavior highly dependent on k_{10}. There is a trivial error associated with one-compartment approximations on Class D drugs.

Dettli's data for digoxin permit a similar comparison for a Class B drug. Assuming a reduction to 50% of normal renal function, the two-compartment calculation would recommend a dose reduction of 31.5%, while the one-compartment calculation would predict 33.3%. Apparently, the relatively low value of k_{10} compared to k_{12} permits k_{10} to be rate limiting, even with such extensive distribution to tissues.

As expected, Class A drugs behave less well than Class D drugs but better than Class C drugs. Two Class A drugs appear in Dettli's table, oxacillin and α-methyldopa. When testing the two methods at 50% of normal renal function, the two- and one-compartment calculations predict a dosage reduction of 36.2 and 41.2% for α-methyldopa and of 32.3 and 37.5% for oxacillin, respectively. These errors are relatively small (14–16%), but they point out that Class A drugs do not transform themselves perfectly into a one-compartment approximation. Careful pharmacokinetic experiments could suffer if a one-compartment approximation were used on a Class A drug.

In light of this classification scheme for drugs, further appreciation can be made of two reports that point out the shortcomings of one-compartment models. MacKichan *et al.* (28) showed how drug clearances of iothalamate and iodohippurate were estimated incorrectly using a one-compartment approximation. They showed graphs with a positive linear relationship between the percentage error in the clearance calculation and the endogenous creatinine clearance. They did not mention what the micro rate constants for these two substances were. The original report (29) showed that in patients with serum creatinine levels of <1.6 mg/100 ml, k_{10}, k_{12}, and k_{21} were 0.54, 1.3, and 1.4 hr^{-1} for iothalamate and 1.6, 1.5, and 1.1 hr^{-1} for iodohippurate, respectively. In subjects with serum creatinine levels of >2.5 mg/100 ml, the micro rate constants for iothalamate were 0.15, 1.5, and 1.4 hr^{-1} and for iodohippurate were 0.6, 1.8, and 1.5 hr^{-1}. The reduced errors reported by MacKichan *et al.* in subjects with low creatinine clearances are explained by noting that the normal sets of rate constants are all of a similar magnitude (Class A or nearly so) while those in subjects with poor renal function would qualify them for Class D, a class where the one-compartment calculations have negligible errors.

Dvorchik and Vesell (30) analyzed a number of drugs to see how the one-compartment model erred in calculations of drug clearances. They noted that for three drugs, diazepam, meperidine, and propranolol, the errors were substantially reduced in patients with hepatic cirrhosis or hypertension compared to controls. Again, in any dysfunction that reduces k_{10}, the drug kinetics will approach a Class D situation more closely and be appropriately handled by a one-compartment model. Because their estimates of error were based on values of α and β rather than on the micro rate constants themselves, it was not clear why certain drugs behaved poorly in one-compartment calculations. The more detailed look used in the present approach shows why ampicillin is the drug most in error according to a one-compartment treatment.

In perspective, most errors caused by a one-compartment approximation will not be clinically significant. If other drugs with a narrower therapeutic range than ampicillin share its kinetic properties, then situations with clinical impact may be more frequent. The purpose of this discussion is to clarify the drug characteristics governing this decision.

The drug classification scheme in Table II points out the importance of detailed knowledge of every drug's pharmacokinetics. Only with information concerning the micro rate constants can one evaluate which pharmacokinetic approach will be valid.

In summary, computer simulations done for their own sake, rather than in the course of fitting experimental data, have been valuable in explaining the pharmacokinetic behavior of drugs described by a two-compartment model. Such understanding is useful both to the pharmacokinetics student and to persons administering drugs who will have a firsthand appreciation of various kinetic situations without having to perform the experiments.

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Ultrafiltration in Serum Protein Binding Determinations

JOHN B. WHITLAM * and KENNETH F. BROWN ˣ

Received January 14, 1980, from the *Department of Pharmacy, University of Sydney, Sydney, N.S.W., Australia.* Accepted for publication May 28, 1980. *Present address: Department of Pharmacy, University of Otago, Dunedin, New Zealand.

Abstract □ The ultrafiltration technique was evaluated theoretically and experimentally for use in clinical serum binding determinations. It is apparent from free energy considerations that the ultrafiltrate concentration approaches the true free concentration only as the pressure gradient causing flow reduces to zero. The theory presented accounts for the previously unexplained lower ultrafiltrate concentration observed at higher filtration pressures. Mathematical simulations of the molecular separation show that the ultrafiltrate concentration remains constant during filtration, and, thus, binding equilibria are not disturbed by this procedure, suggesting that an arbitrary restriction on the volume filtered is unnecessary. This finding greatly extends the value of the ultrafiltration technique in clinical binding determinations, especially for strongly bound, potent drugs where assays may be insufficiently sensitive to detect the extremely small free fractions reliably. These theoretical findings were verified experimentally by ultrafiltration of salicylate, ibuprofen, and carprofen in buffer, purified proteins, and whole serum.

Keyphrases □ Ultrafiltration—evaluation for use in clinical serum binding determinations □ Binding—evaluation of ultrafiltration technique for use in clinical serum binding determinations □ Salicylate—determination of serum binding by ultrafiltration □ Ibuprofen—determination of serum binding by ultrafiltration

Interest in the influence of plasma binding on drug disposition is increasing. The extent of binding partially controls drug distribution between the blood and extravascular fluids (1, 2) and may profoundly affect both hepatic and renal clearance (3, 4). Furthermore, there is ample evidence that the free fraction of drug may be substantially altered postoperatively (5), in the elderly (6), and following stress and disease (7) and, for certain drugs, may differ considerably with the plasma concentration and between individuals (8, 9).

BACKGROUND

Reliable routine methodology for estimating the fraction of free drug in plasma and whole blood is needed. Ultrafiltration appears to be more appropriate than dialysis techniques because it can be carried out rapidly without storage or addition of potentially competitive buffer components and electrolytes. The speed with which the free fraction can be estimated after sample collection is particularly important since the levels of fatty acids produced by lipolysis of triglycerides increase on storage (10) and during dialysis (11). Nonesterified fatty acids are known to decrease the binding of drugs *in vitro* (12) and *in vivo* (13).

Among the generally recognized limitations of the ultrafiltration technique are the polarization of protein on the membrane, the uptake of small molecules by the membrane, and the change in the protein concentration with the volume filtered. Polarization may be minimized by stirring, and membrane binding may be assessed independently. However, the influence of filtration pressure in selectively altering the transport of solvent and drug molecules is not widely appreciated. Furthermore, in estimating the extent of binding by molecular filtration, it has become accepted practice to ultrafilter only a small fraction of the total sample (often <10%) to avoid disturbance of the protein binding equilibria (14–17). The subsequent difficulty in estimating extremely small amounts of ultrafiltered drug (18) often presents insurmountable analytical problems, particularly with strongly bound, low serum concentration drugs.

This report discusses two important aspects of ultrafiltration. First, the influence of filtration pressure on the ultrafiltrate drug concentration is examined theoretically. The theory presented accounts for the previously unexplained dilution of the ultrafiltrate observed at higher filtration pressures by Spector *et al.* (19). Second, it is shown theoretically and

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