Effects of Change in Elimination on Various Parameters of the Two-Compartment Open Model

WILLIAM J. JUSKO*▲ and MILO GIBALDI†

Abstract □ The various parameters of the two-compartment open model which are employed commonly in pharmacokinetics can be classified into three groups, based on their mathematical behavior, when a change in the elimination constant (k_{el}) is induced but the distribution constants (k_{12}, k_{21}, and V_c) of the drug are maintained unchanged. At a given dose of drug, certain parameters (V_{DSS} and C_p^0) remain constant because they are independent of k_{el}. Other parameters (Area, Cl_B, D_1, D_2, and D_T) change exactly in proportion of k_{el} because these values are a direct linear function of k_{el}. A third group (α, β, A, B, $V_{D\beta}$, $V_D$area, V_B, f_c, and $t_{1/2\beta}$) are nonlinear or hybrid parameters; they change in value disproportionately with k_{el}. Absolute changes in distribution space or elimination constants at a given dose level cannot be quantitated with these hybrid terms individually. They reflect the degree of equilibration of a drug between compartments and should be restricted to use as proportionality terms for relating the time course of plasma and body levels of drug.

Keyphrases □ Two-compartment open model—effect of changes in elimination on pharmacokinetic parameters □ Pharmacokinetics, two-compartment open model—effects of changes in elimination □ Elimination effects—two-compartment open-model parameters

One of the most common perturbations of a pharmacokinetic system is that involving a change in elimination, with or without a secondary effect on the distribution of a drug. For example, decreased renal excretion of drugs is expected in patients with renal failure or when probenecid, an inhibitor of renal tubular transport of organic acids, is administered with most penicillins. Increased metabolism, on the other hand, is often observed with phenobarbital pretreatment which causes induction of drug-metabolizing enzymes. In each case, modification of the time course of body levels of drug occurs, but interpretation of this change is dependent on the pharmacokinetic model employed and an understanding of the mathematical and physiological basis of the model.

A specific problem which has occurred involves the interpretation of the apparent change in the volume of distribution of several penicillins when probenecid is administered (1, 2). Although it has been recognized that a decrease in elimination produced by inhibition of renal tubular secretion is the primary cause for the increased plasma and body levels of the antibiotic, a change in the apparent volume of distribution has been suggested as a secondary effect of probenecid. One purpose of this report is to reconsider the effects of changing the elimination rate constant of a drug on the various derived parameters of the two-compartment open model. It can be shown that alteration of elimination produces a change in the *degree of equilibration* of a drug between the central and peripheral compartments. Although this alteration affects certain apparent "volume of distribution" parameters, no change in distribution mechanisms or space necessarily occurs. However, the change in compartmental equilibration is likely to affect the time course of the pharmacological effect of a drug since the relationship between plasma levels and "tissue" levels of the drug is modified. In evaluating data that are best described with a two-compartment open model, several parameters can be classified as "hybrid" in that they change disproportionately with the change in the elimination or distribution rate constant. Because of this behavior, it is desired to point out where caution is needed in interpretation of the various constants and parameters of the routinely employed one- and two-compartment models.

TWO-COMPARTMENT OPEN MODEL

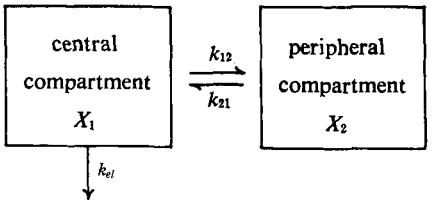
The type of data usually fitted with a two-compartment open model are plasma concentrations and urinary excretion rates, which decline in a biexponential manner after intravenous administration of a drug. If the investigator has some physiological basis for assuming that drug elimination occurs solely from the central compartment, then the model employed is shown in Scheme I. First-order mass transfer (distribution) rate constants between the central (X_1) and peripheral (X_2) compartments are k_{12} and k_{21}, while the overall rate constant for drug elimination by various routes is k_{el}. These rate constants, as well as the volume of the central compartment (V_c), are derived from the biexponential plasma concentration (C_p) data:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

where A and B are zero-time plasma concentration intercepts, and α and β are related to the slopes of the disposition curve. In addition to V_c and the above rate constants, a number of other calculated parameters have appeared in the literature. These include:

- C_p^0 = extrapolated zero-time plasma concentration of drug (*i.e.*, $A + B$)
- Area = total area under linear plasma concentration–time curve (*i.e.*, from time zero to ∞)
- Cl_B = body clearance (equal to the sum of all clearance processes in the body)
- $t_{1/2\beta}$ = half-life of β-phase of drug disposition
- f_c = fraction of that drug in the body which is located in the central compartment
- V_{DSS} = steady-state volume of distribution as introduced by Riggs (3)
- $V_{D\beta}$ = pseudoequilibrium (β-phase) volume of distribution as introduced by Gibaldi *et al.* (4)
- $V_D$area = volume of distribution calculated from the Area (5)
- V_B = apparent volume of distribution obtained by neglecting the α- or distributive phase of drug disposition (5)
- D_1, D_2, D_T = integral coefficients for the central (D_1) and peripheral (D_2) compartments and the whole body (D_T) as introduced by Jusko *et al.* (6) (These values, when multiplied by the dose, provide the amount *versus* time area or integral for the particular compartment.)

Methods of calculation of these parameters are shown in Table I.



Scheme I

Effects of Changes in Elimination—Determination of the effect of changes in elimination on the various parameters of the two-compartment open model was made by presetting the values of k_{12}, k_{21}, V_c, and dose, calculating numerical results for the remaining parameters at several k_{el} values, and examining the fundamental interrelationships of the equations used to describe the model. The k_{el} values were varied numerically over four orders of magnitude and, in addition, the parameter limits were determined at the extremes of k_{el} as shown in Table I. Changes in k_{el} did not affect the calculated values of C_p^0 and V_{DSS} because these parameters, as well as k_{12}, k_{21}, and V_c, are mathematically independent of the value of k_{el}. The values of Area, Cl_B, D_1, D_2, and D_T change exactly in proportion to k_{el}. This occurs because each of these parameters is a direct *linear* function of k_{el} and one or more other constants, which are also independent of k_{el}. The remaining parameters can be classified into a third group because their values change disproportionately with the magnitude of k_{el}. These parameters are: α, β, A, B, $t_{1/2\beta}$, f_c, $V_{D\beta}$, $V_D$area, and V_B. The disproportionality is accounted for by the fact that the latter parameters are derived from a *nonlinear* function of k_{el}, as can be seen readily from the definitions of α and β in Table I. Similar conclusions concerning the mathematical behavior of the hybrid pharmacokinetic terms can be reached if k_{el} is assumed to remain constant and either k_{12} or k_{21} is varied. The hybrid parameters, therefore, should not be used individually as a direct or sole measure of a change in drug elimination or distribution.

Of practical importance, the apparent volume of distribution parameters, $V_{D\beta}$, $V_D$area, and V_B, greatly increase in value as k_{el} is increased, particularly when k_{el} exceeds the value of k_{21}. However, by definition of the system (k_{12}, k_{21}, and V_c remaining constant), these hybrid parameters do not reflect changes in distribution rate constants or space. On the other hand, it was shown previously (4, 7–9) that the $V_{D\beta}$ term serves an extremely useful function as a proportionality factor between drug in the body (X_B) and β-phase plasma concentrations ($C_{p\beta}$)—*viz:*

$$X_B = V_{D\beta} \cdot C_{p\beta} \qquad \text{(Eq. 2)}$$

Furthermore, it was shown (2, 9) that when the elimination rate of the drug is decreased, the fraction of the amount in the body indeed seems to shift so that more is located in the central compartment during the β-phase.

Another rationale for the nonlinear behavior of the hybrid volume terms and f_c involves consideration of equilibria in the two-compartment system. When drug elimination is very slow ($k_{el} \to 0$), the drug can approach or reach an equilibrium between the central and peripheral compartments. In such case, a true steady state is reached and thus:

$$f_c ss = \frac{k_{21}}{k_{21} + k_{12}} \qquad \text{(Eq. 3)}$$

as shown by the first limit for f_c in Table I. In this situation, all of the apparent total volume of distribution terms converge to a minimum value and become identical to V_{DSS}, as can be noted from the volume parameters listed in Table I. In such case, it makes little difference whether $V_{D\beta}$ or V_{DSS} is used to relate plasma and body levels of drug using Eq. 2.

At the other extreme, when drug elimination is very rapid, little of the drug has an opportunity to reach the peripheral compartment

Table I—Behavior of Various Parameters of the Two-Compartment Open Model as the Elimination Constant (k_{el}) is Changed (Parameters Maintained Constant: k_{12} = 1.0 hr.$^{-1}$, k_{21} = 1.5 hr.$^{-1}$, V_c = 12 l., and Dose = 3 g.)

Parameter	Method of Calculation	Limit: $k_{el} \to 0$	k_{el}, hr.$^{-1}$ 0.01	0.1	1.0	10.0	Limit: $k_{el} \to \infty$
α	$\frac{1}{2}\cdot(b + \sqrt{b^2 - 4\cdot k_{21}\cdot k_{el}}$ where $b = k_{12} + k_{21} + k_{el}$	$k_{12} + k_{21}$	2.50	2.541	3.00	11.16	∞
β	$\frac{1}{2}\cdot(b - \sqrt{b^2 - 4\cdot k_{21}\cdot k_{el}})$	0	0.006	0.059	0.50	1.345	k_{21}
A	$\frac{D_0\cdot(k_{21} - \alpha)}{V_c\cdot(\beta - \alpha)}$	$\frac{D_0\cdot k_{12}}{V_c\cdot(k_{12} + k_{21})}$	0.100	0.105	0.15	0.246	$\frac{D_0}{V_c}$
B	$\frac{D_0\cdot(k_{21} - \beta)}{V_c\cdot(\alpha - \beta)}$	$\frac{D_0\cdot k_{21}}{V_c\cdot(k_{12} + k_{21})}$	0.150	0.145	0.10	0.004	0
C_p^0	$A + B = D_0/V_c$	D_0/V_c	0.25	0.25	0.25	0.25	D_0/V_c
Area	$\frac{A}{\alpha} + \frac{B}{\beta} = \frac{D_0}{V_c\cdot k_{el}}$	∞	25.0	2.50	0.25	0.025	0
Cl_B	$k_{el}\cdot V_c$	0	0.12	1.2	12.0	120.0	∞
$t_{1/2\beta}$	$0.693/\beta$	∞	115	11.5	1.4	0.51	0
f_c	β/k_{el}	$k_{21}/(k_{12} + k_{21})$	0.6	0.59	0.50	0.13	0
V_{DSS}	$\frac{(k_{12} + k_{21})V_c}{k_{21}}$	$\frac{(k_{12} + k_{21})V_c}{k_{21}}$	20.0	20.0	20.0	20.0	$\frac{(k_{12} + k_{21})\cdot V_c}{k_{21}}$
$V_{D\beta}$	$k_{el}\cdot V_c/\beta$	V_{DSS}	20.0	20.3	24.0	89.2	∞
$V_D$area	$D_0/\text{Area}\cdot\beta$	V_{DSS}	20.0	20.3	24.0	89.2	∞
V_B	D_0/B	V_{DSS}	20.0	20.7	30.0	75.0	∞
D_1	$\int_0^\infty X_1\cdot dt/D_0 = 1/k_{el}$	∞	100.0	10.0	1.0	0.1	∞
D_2	$\int_0^\infty X_2\cdot dt/D_0 = \frac{k_{12}}{k_{21}\cdot k_{el}}$	∞	66.7	6.67	0.667	0.0667	0
D_T	$\int_0^\infty X_B\cdot dt/D_0 = \frac{k_{12} + k_{21}}{k_{21}\cdot k_{el}}$	∞	166.7	16.67	1.667	0.1667	0

Table II—Effect of Probenecid on Distribution and Elimination of Benzylpenicillin[a]

Parameter, Units	Mean Values (*SD*)		Statistical Difference[b]: *t* (*p*)
	Control	Probenecid	
A, mcg./ml.	294 (151)	182 (35)	1.93 (NS)
B, mcg./ml.	61 (29)	184 (51)	−4.86 ($p < 0.005$)
α, hr.$^{-1}$	4.02 (1.48)	4.63 (3.44)	−0.50 (NS)
β, hr.$^{-1}$	0.944 (0.082)	0.737 (0.172)	3.66 ($p < 0.025$)
C_p^0, mcg./ml.	355 (160)	366 (77)	−0.19 (NS)
Area, mcg. hr./ml.	142 (53)	322 (96)	−6.70 ($p < 0.005$)
Cl_B, ml./min.	408 (183)	166 (42)	3.71 ($p < 0.025$)
$t_{1/2\beta}$, hr.	0.74 (0.06)	0.98 (0.23)	−2.87 ($p < 0.05$)
f_c	0.397 (0.146)	0.637 (0.135)	−8.80 ($p < 0.005$)
V_c, l.	9.7 (3.6)	8.5 (1.7)	1.02 (NS)
V_{DSS}, l.	15.2 (5.7)	12.0 (2.6)	1.93 (NS)
$V_{D\beta}$ or $V_D$area, l.	25.8 (11.2)	13.6 (2.9)	3.12 ($p < 0.05$)
V_B, l.	58.9 (25.5)	17.3 (4.4)	3.84 ($p < 0.025$)
k_{12}, hr.$^{-1}$	0.93 (0.71)	1.57 (1.70)	−1.04 (NS)
k_{21}, hr.$^{-1}$	1.44 (0.16)	2.60 (1.56)	−1.67 (NS)
k_{el}, hr.$^{-1}$	2.59 (0.73)	1.20 (0.35)	5.83 ($p < 0.005$)
D_1, hr.	0.42 (0.17)	0.92 (0.38)	−4.86 ($p < 0.025$)
D_1a, hr.[c]	0.33 (0.16)	0.71 (0.32)	−4.28 ($p < 0.025$)
D_2, hr.	0.22 (0.11)	0.33 (0.24)	−1.59 (NS)
D_T, hr.	0.65 (0.14)	1.25 (0.30)	−8.00 ($p < 0.005$)
D_{Ta}, hr.[c]	0.55 (0.12)	1.04 (0.26)	−7.39 ($p < 0.005$)

[a] Data from Gibaldi *et al.* (2). [b] Method of paired comparisons; $DF = 4$. [c] Corrected for protein binding (6), thus reflecting "available" drug.

prior to its removal from the body. Since drug in the central compartment disappears rapidly when k_{el} is large, the value of f_c approaches zero and the hybrid volume terms diverge from V_{DSS} (Table I). The awkward situation is thus encountered where $V_{D\beta}$ is required to relate β-phase plasma and body levels of drug, but the β-phase controls very little of the amount of time course or drug in the body. It, therefore, becomes of interest to consider the relationship:

$$\int_0^\infty X_B\,dt = V_{DSS}\int_0^\infty C_p\,dt \qquad \text{(Eq. 4)}$$

which can be derived from the equations for Area and D_T listed in Table I. From this expression, it follows that V_{DSS} can serve as a general proportionality constant between *average* body levels ($\bar{X}_B$) and *average* plasma levels ($\bar{C}_p$) of drug after a single dose in the manner:

$$\bar{X}_B = V_{DSS}\cdot\bar{C}_p \qquad \text{(Eq. 5)}$$

This is of importance in the commonly encountered situation with many penicillin antibiotics where the α-phase accounts for removal of most of the drug from the body. In addition, when drug is given by constant-rate intravenous infusion or by multiple dosing, the two-compartment system can reach a steady-state equilibrium and the value of V_{DSS} is again required to relate $\bar{C}_p$ and $\bar{X}_B$ (8, 9).

Comparison of the integral coefficient data in Table I indicates that the amount-time product of drug in both the central and peripheral compartments is expected to change in inverse proportion to alteration of k_{el}. However, the ratio of integrals:

$$\frac{D_1}{D_2} = \frac{\int_0^\infty X_1\,dt/D_0}{\int_0^\infty X_2\,dt/D_0} = \frac{k_{12}}{k_{21}} \qquad \text{(Eq. 6)}$$

does not vary as k_{el} is modified unless the value of either k_{12} or k_{21} also changes. It is, therefore, evident that the increase in f_c as k_{el} decreases occurs only during the β-phase and does not reflect increased overall retention of drug in the central compartment at the expense of the peripheral compartment; it only shows that the amount *versus* time curves for X_1 and X_2 are both modified in *shape* similar to changing the mode of administration of the drug (8).

An important distinction can, therefore, be made in the use and terminology involving distribution volumes and constants. Parameters such as V_{DSS}, V_c, k_{12}, and k_{21} can be used to determine actual changes in distribution space or rates. Hybrid volume terms such as $V_{D\beta}$, $V_D$area, or V_B do not reflect the distribution space of a drug and should not be used for this purpose. The hybrid "volumes" should be restricted to use as proportionality factors between β-phase plasma concentrations (C_p) and body levels (X_B) of drug after intravenous dosage of drug since these parameters are affected by the *degree of equilibration* of drug between the plasma and tissue compartments. Their importance in pharmacokinetics thus varies with drugs and the degree to which the β-phase controls the time course of drug disposition. Similar and previous (10) considerations make it apparent that the β-half-life does not accurately reflect a change in elimination and may, in fact, better represent the value of k_{21} when k_{el} is very large (Table I).

ONE-COMPARTMENT MODEL

The effects of changes of k_{el} on hybrid distribution and elimination parameters are of critical importance when an attempt is made, using a one-compartment system, to fit data best represented with a two-compartment model. In such a case, for example, one might observe a change in the plasma level area when elimination is altered and characterize the data with the equation:

$$\text{Area} = \frac{1.44\cdot D_0\cdot t_{1/2}}{V} \qquad \text{(Eq. 7)}$$

where V, the apparent volume of distribution, is equivalent to $V_{D\beta}$ or $V_D$area (4); and $t_{1/2}$, the apparent disposition half-life, is equal to $0.693/\beta$. Since, by definition, both V and $t_{1/2}$ are actually hybrid parameters, neither is useful for quantitating true changes in distribution space or elimination rates. On the other hand, their combination can be of value for predicting plasma drug levels at the given dose and elimination rate (9, 10).

Since the product or quotient of two hybrid parameters often yields either an absolute or proportional pharmacokinetic constant[1], limited plasma level data from an experiment can be better evaluated by calculating the body clearance (Cl_B) where:

$$Cl_B = \frac{0.693\cdot V}{t_{1/2}} = \beta\cdot V = k_{el}\cdot V_c \qquad \text{(Eq. 8)}$$

Both the Area and Cl_B values will be proportional to the change in

[1] Several examples can be noted from "Methods of Calculation" in Table I.

the elimination constant (k_{el}), because neither parameter is affected by a change in the distribution equilibrium. However, both values can be altered by a change in distribution rate constants or space, a phenomenon that cannot be accurately quantitated with the hybrid values of V and $t_{1/2}$ from the limited model. Therefore, parameters of a one-compartment model derived from data from a two-compartment system cannot be used to distinguish "real" changes in *both* elimination and distribution of a drug. Only the net effect of both perturbations can be measured when the model is oversimplified.

Effect of Probenecid on Benzylpenicillin Pharmacokinetics—Gibaldi *et al.* (2) measured penicillin concentrations in the serum after intravenous administration of benzylpenicillin during probenecid therapy. These data were subjected to pharmacokinetic analysis according to the two-compartment model shown in Scheme I along with the equations, or derivations thereof, listed in Table I. The results of these calculations are shown in Table II. With probenecid treatment, the plasma level areas increased more than twofold but the β-half-life of the antibiotic was only slightly longer. The distribution rates and space of penicillin do not appear to be significantly altered by probenecid since the transfer rate constants (k_{12} or k_{21}) and the apparent volumes of distribution (V_c and V_{DSS}) were essentially unchanged. The decrease in the elimination rate constant was the primary change occurring in the stable pharmacokinetic parameters. Although this appears evident from the comparative data listed in Table II, the absence of an effect of probenecid on interaction of these parameters was also ruled out by applying multiple linear regression analysis (11) to the data. The change in plasma level area was used as the independent variable to correlate simultaneously with the changes in k_{el}, k_{12}, k_{21}, and V_c values. The only significant correlation was between Area and k_{el} ($r = 0.873$, $p = 0.05$).

Several secondary effects of the change in the elimination rate constant of penicillin can be noted from the results in Table II. The total body level integral (D_T) of penicillin, even when corrected for protein binding (D_{Ta}), was twice as large with probenecid. This was caused by the relatively similar change in magnitude of the elimination constant. The f_c and $V_{D\beta}$ values also changed twofold when probenecid was given, and the decrease in $V_{D\beta}$ is a reflection that the system was closer to reaching steady-state equilibrium with probenecid. This also indicates that, at equal plasma concentrations during the β-phase, more of the drug in the body will be located in the central compartment with probenecid treatment. Since the integral coefficients for the central and peripheral compartments are expected to increase in proportion to the decrease in k_{el} unless the value of V_c, k_{12}, or k_{21} also changes, a slight, but not statistically significant, change in distribution rates into or from the peripheral compartment is suspected because the value of D_2 did not increase proportionally as much as k_{el} decreased. Physiologically, a slight change in the penicillin distribution rate is reasonable since probenecid is capable of inhibiting anion transport into other tissues as well as the kidney (12). The general conclusion concerning the effect of probenecid on the chemotherapeutic properties of benzylpenicillin is that a given dose of the antibiotic should be twice as effective with probenecid since the total body integral coefficient increases twofold (6). This, however, requires experimental verification.

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▲ To whom inquiries should be directed.