Drug Elimination and Apparent Volume of Distribution in Multicompartment Systems

MILO GIBALDI▲ and DONALD PERRIER

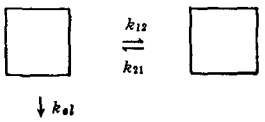
Abstract □ A relationship between drug distribution and elimination in multicompartment systems has been demonstrated, which suggests that under certain conditions a decrease in the elimination rate constant (k_{el}) results in a significant decrease in the apparent volume of distribution. The mathematical relationships are consistent with experimental findings as to the effect of probenecid or renal failure on drug distribution. The implications of a change in the apparent volume of distribution, in patients with impaired renal function or with other conditions resulting in reduced drug elimination, with respect to "dose"–response relationships, estimation of bioavailability and absorption rate, the relationship between biologic half-life and impairment of elimination processes, and the use of creatinine clearance measurements as a guide to the design of dosage regimens in patients with renal disease are considered.

Keyphrases □ Drug distribution and elimination—relationship in multicompartment systems, effect on apparent volume of distribution □ Elimination and drug distribution—relationship in multicompartment systems, effect on apparent volume of distribution □ Volume of distribution, apparent—considerations relative to drug distribution and elimination relationship in multicompartment systems

Certain clinical conditions which result in reduced drug elimination often produce a decrease in the apparent volume of drug distribution (1–3). For example, administration of probenecid, a potent inhibitor of renal tubular secretion of organic acids, substantially reduces the apparent volume of distribution of various penicillin derivatives in man (1). Pharmacokinetic analysis of drug concentrations in the serum of normal human subjects and of patients with renal failure after administration of cephalexin, colistimethate, lincomycin, methicillin, or insulin reveals that a significant reduction in the apparent distribution of each drug accompanies the anticipated increase in half-life in patients with an impaired renal function (3).

THEORETICAL

Analysis of penicillin concentrations in the serum after intravenous administration of benzylpenicillin to five patients during probenecid therapy and during control periods, according to the two-compartment open model shown in Scheme I, produced the



Scheme I

following results (2):

1. Probenecid decreased k_{el} by 50% compared to control values.
2. In accord with previous findings with other penicillins, probenecid decreased the apparent volume of distribution of benzylpenicillin by about 40%.
3. Probenecid had no effect on the volume of the central compartment (V_c) of benzylpenicillin.
4. Probenecid had no significant effect on the distribution rate constants for benzylpenicillin and, in fact, k_{12}/k_{21} was virtually identical in control patients and in patients receiving probenecid.

These findings, particularly points 3 and 4, strongly suggest that the decrease in the apparent distribution of certain drugs in the face of reduced elimination has a pharmacokinetic rather than a physiologic basis. A detailed mathematical analysis of certain properties of multicompartment models, presented herein, indicates clearly that this is the case. The various relationships and simulations were developed based on the two-compartment open model shown in Scheme I. In principle, however, the results are model independent given the constraint that the plasma, serum, or blood is part of the same compartment from which drug elimination occurs exclusively.

After intravenous administration of most drugs, the drug concentration in the plasma declines in a multiexponential fashion. The slope of the *terminal* exponential phase, as determined from appropriate semilogarithmic plots, is defined as $-\beta/2.303$. In turn, the biological half-life of a drug is given by $0.693/\beta$ (4). It has been shown for multicompartment open models, such as the one depicted in Fig. 1, that:

$$\beta = f_c \cdot k_{el} \qquad \text{(Eq. 1)}$$

where f_c is the fraction of drug in the body that is present in the central compartment (5). In the "postdistributive" or terminal exponential phase of drug elimination, f_c is independent of time but dependent on k_{el}, since (for the two-compartment open model) (5):

$$f_c = \frac{k_{21} - (k_{21}k_{el}/\alpha)}{\alpha - k_{el}} = \frac{k_{21}}{\alpha} \qquad \text{(Eq. 2)}$$

where:

$$\alpha = {}^1/_2[(k_{12} + k_{21} + k_{el}) + \sqrt{(k_{12} + k_{21} + k_{el})^2 - 4k_{21}k_{el}}] \qquad \text{(Eq. 3)}$$

Accordingly, a plot of β *versus* k_{el} is curvilinear, as shown in Fig. 1. with β asymptotically approaching k_{21} as k_{el} approaches infinity[1], It is quite apparent that the instantaneous slope of this plot, *i.e.*, f_c, increases as k_{el} decreases.

A proportionality constant, $(V_d)_\beta$, has also been defined (5) for multicompartment systems to relate drug concentration in the plasma to the total amount of drug in the body at any time after attainment of pseudodistribution equilibrium (*i.e.*, during the terminal exponential phase of drug elimination) such that:

$$(V_d)_\beta = V_c/f_c \qquad \text{(Eq. 4)}$$

where V_c is the volume of the central compartment. Of particular importance is the fact that $(V_d)_\beta$ is absolutely equivalent to the apparent volume of distribution (V) of a drug as determined by the area equation (5, 6):

$$V = 1.44 \cdot D \cdot t_{1/2}/A \qquad \text{(Eq. 5)}$$

where D is the amount of drug absorbed, $t_{1/2}$ is the biologic half-life, and A is the area under the drug concentration in the plasma *versus* time curve from $t = 0$ to $t = \infty$. It is evident from Eq. 4 that $(V_d)_\beta$ and, therefore, V will decrease with an increase in f_c.

The mathematical relationships developed here are totally consistent with experimental findings. As predicted, a reduction in the elimination rate constant (k_{el}) of certain drugs caused by coadministration of probenecid or renal failure results in increased values of

[1] As $k_{el} \rightarrow \infty$, $\alpha \rightarrow k_{el}$ (Eq. 3). Since $\alpha\beta = k_{21}k_{el}$, then as $\alpha \rightarrow k_{el}$, $\beta \rightarrow k_{21}$.

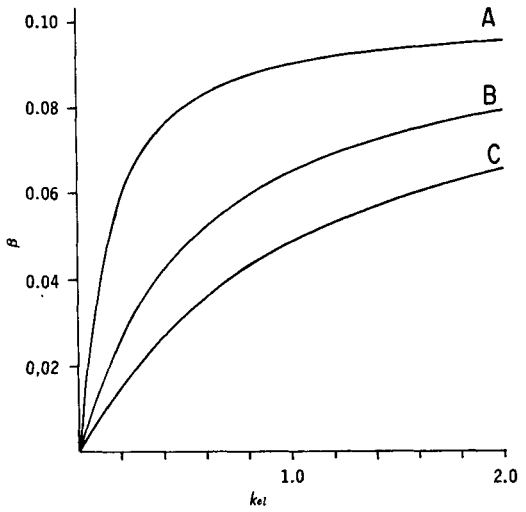


Figure 1—*Curvilinear relationship between β and* k_{el} *in two-compartment open model. Key: A,* $k_{21} = 0.1$, $k_{12} = 0.1$; *B,* $k_{21} = 0.1$, $k_{12} = 0.5$; *and C,* $k_{21} = 0.1$, $k_{12} = 1.0$.

f_c and decreased values of V compared to control values (1–3). No effects on V_c, k_{12}, or k_{21} need be postulated to rationalize the clinical data.

A number of simulations were made to determine the magnitude of the change in V with respect to a change in k_{el} under different conditions of distribution. Values of f_c were calculated under "normal" conditions ($k_{el}^N = 0.5$ time^{-1}) and under conditions of "reduced drug elimination" ($k_{el}^R = 0.1$ time^{-1}). From these data the change in V as a function of decreased drug elimination was calculated. Values of k_{21}/k_{el}^N ranged from 0.1 to 20, while values of k_{12}/k_{21} ranged from 0.1 to 50. The results are shown in Table I. Under the conditions of the simulation, appreciable effects on V were observed only when $k_{21}/k_{el}^N \leq 1$. However, at a given value of k_{21}/k_{el}^N, the effects on V are apparently diminished with an increase in k_{12}/k_{21}.

It is likely that the apparent volume of distribution of drugs with large elimination rate constants (k_{el}) and/or drugs whose overall elimination from the body is largely mediated by the mass transfer rate constant from the tissue compartment, *i.e.*, k_{21}, will be substantially reduced under various clinical conditions that diminish drug elimination. Such conditions might include disease states such as renal failure and hepatic and cardiac insufficiency, as well as the coadministration of agents such as probenecid (which reduces active tubular secretion) or phenyramidol (which appears to inhibit the metabolism of certain drugs). The relationships developed here also indicate that the enhanced elimination of certain drugs as would occur on coadministration of microsomal enzyme-inducing agents such as phenobarbital may result in an increased apparent volume of distribution. Several experimental observations suggest that this might be so (7, 8).

DISCUSSION

The clinical implications of a diminished distribution in patients with a reduced ability to eliminate certain drugs are quite interesting. For example, a given drug concentration in the plasma of patients with renal failure may represent substantially less total drug in the body than the same concentration in normal subjects. It follows that if the site of a pharmacologic response resides within the "tissue" compartment, then the same drug concentration in the plasma of renal failure patients and normal subjects may produce an appreciably less intense clinical response in the group with impaired renal function. Estimates of bioavailability or absorption rate in subjects with impaired ability to eliminate drugs may be in error unless the changes in V as well as biologic half-life are taken into account in the calculations.

A particularly interesting consequence of the relationship between drug elimination and apparent volume of distribution is that the body, by virtue of its multicompartment nature, passively compensates (at least in part) for an impaired elimination function by shifting a larger fraction of drug in the body to the compartment from which elimination takes place. Hence, a significant decrease in k_{el} may be offset by an increase in f_c, so the net effect on biologic half-life is negligible. An excellent example is nafcillin elimination in subjects receiving probenecid. Probenecid markedly reduces the elimination rate constant (k_{el}) of this penicillin derivative. However, the biological half-life of nafcillin is identical in subjects receiving probenecid and in control subjects (1). This compensatory phenomenon may help explain why hepatic impairment appears to have little effect on the biological half-life of certain drugs eliminated predominantly by liver metabolism (9).

Table I—Effect of Impaired Elimination on f_c and V

k_{21}	k_{12}	$k_{el} = 0.5$, f_c	$k_{el} = 0.1$, f_c	$k_{el} = 0.1$, V^a
10	10	0.494	0.499	0.99
1.0	1.0	0.438	0.488	0.90
0.5	0.5	0.382	0.475	0.80
0.1	0.1	0.162	0.382	0.42
0.05	0.05	0.090	0.293	0.31
1.0	10	0.087	0.090	0.97
1.0	5.0	0.156	0.164	0.95
1.0	1.0	0.438	0.488	0.90
1.0	0.2	0.757	0.822	0.92
1.0	0.1	0.852	0.901	0.95
0.1	5.0	0.019	0.020	0.95
0.1	1.0	0.064	0.084	0.76
0.1	0.5	0.095	0.146	0.65
0.1	0.1	0.162	0.382	0.42
0.1	0.01	0.195	0.730	0.27

[a] Apparent volume of distribution expressed as a fraction of volume when $k_{el} = 0.5$.

Since the nonlinear relationship between k_{el} and β raises some questions concerning the use of creatinine clearance as a guide to the design of dosage regimens in patients with impaired renal function, it is imperative to consider these questions. Dettli (9) and Dettli *et al.* (10) proposed a linear relationship between endogenous creatinine clearance (Cl) and β, assuming single-compartment kinetics. However, in a multicompartment system, one might expect a linear relationship between Cl and k_{el} but a curvilinear relationship between Cl and β. Theory predicts that for certain drugs a very marked curvilinear relationship between β and Cl may exist such that interpolation of β between the values found in normal subjects and those observed in anuric subjects will result in a serious underestimate of β which, in turn, could lead to undermedication. Clearly, the use of a linear approximation between β and Cl is not likely to lead to overmedication. Extensive examination of literature reports on half-lives of various drugs in patients with varying degrees of renal impairment leads us to suggest that the data used for the β–Cl correlations are sufficiently scattered so as to prevent the differentiation of a linear from a curvilinear relation. Hence, despite the implications of the proposed theory, there is little evidence at this time to question the general utility in clinical practice of creatinine clearance measurements for designing dosage regimens in patients with renal impairment.

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Preliminary Phytochemical Investigation of *Euphorbia millii*

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Abstract □ *Euphorbia millii* (Des Moulins) was investigated. β-Sitosterol, cycloartenol, and β-amyrin acetate were isolated from the petroleum ether extract. The presence of lupeol and euphol as minor constituents was demonstrated by GC, and the existence of flavonoids in the methanol extract was shown.

Keyphrases □ *Euphorbia millii*—phytochemical investigation, isolation and identification of constituents □ Medicinal plants—preliminary phytochemical investigation of *Euphorbia millii* □ GC—isolation and identification of *Euphorbia millii* constituents

Euphorbia millii (Des Moulins) is a native shrub of the Island of Madagascar and is widely cultivated as an ornamental plant in the South Florida area. It has been reported (1) to contain toxic substances in its latex.

The genus *Euphorbia* has been very prolific in the production of substances with biological properties. Antitumor activity has been reported in extracts of *Euphorbia drumondii* (2), antimicrobial alkaloids have been found in *Euphorbia thymifolia* (3), and extracts from *Euphorbia ingens* (4) have produced epidermal hyperplasia and tumors in mice.

In addition, a variety of chemical compounds have been isolated from *Euphorbia* species. Dumkow (5) isolated kaempferol 3-α-monorhamnopyranoside from *Euphorbia myrsinites*, Wingnes and Andrew (6) reported the presence of D-glucaric acid in the latex of *Euphorbia canariensis*, and Morales Mendez (7) identified triterpenoids in *Euphorbia caracasana*.

Interest in this investigation arose out of the limited phytochemical reports on *E. millii* and the many medicinal applications of other species from the genus *Euphorbia*.

EXPERIMENTAL

Plant Material—The plants[1] used in this investigation were air dried for 1 month and then ground in a mill (Fitzpatrick), yielding 2.4 kg. of fine, powdered material.

[1] Obtained from Melrose Nursery, Miami, Fla., during the spring of 1969.

Table I—Chromatography on Silicic Acid of the Petroleum Ether Extract

	Fraction Number	Fraction Weight, g.	Eluent	L.B. Test[a]
A	(1–22)	18.4	Heptane–benzene (1:1)	–
B	(23–28)	5.2	Heptane–benzene (1:1)	+
C	(29–39)	18.6	Benzene	+
D	(40–43)	3.4	Benzene	+
E	(44–55)	14.0	10% Ethyl acetate in benzene	+
F	(56–63)	8.4	10% Ethyl acetate in benzene	+
G	(64–79)	13.9	20% Ethyl acetate in benzene	–

[a] Liebermann–Burchard test.

Extraction of Powdered Plant—The fine, powdered material was extracted in a 3-l. soxhlet apparatus with petroleum ether (b.p. 30–60°) for 72 hr. At the end of this period, the petroleum ether was removed and the marc was extracted with methanol for an additional 72 hr.

The petroleum ether extract was evaporated to dryness with the aid of a continuous circulating-type evaporator and a rotavapor (Bachi). The gummy, greenish residue obtained (196 g.) was then subjected to saponification.

Saponification of Petroleum Ether Extract—Before saponification of the petroleum ether extract was undertaken, tests for the presence of sterols were performed on the extract. Samples were subjected to the Liebermann–Burchard and Salkowski tests (8, 9), giving positive reactions characteristic of steroids or triterpenoid-type compounds.

The gummy residue obtained from the petroleum ether extraction was dissolved in 1.5 l. of ethanol and saponified by refluxing with 30 g. of potassium hydroxide for 1.5 hr. The ethanol was then removed with the help of the rotavapor, and the residue was mixed with 1.5 l. of water. The water suspension was placed in a 2-l. separator and extracted with six 500-ml. portions of ether. The ether fraction was tested for the presence of sterols with the Liebermann–Burchard reagent and gave a positive test. The solvent was then evaporated and the residue was dissolved in 1 l. of hot acetone. Thirteen grams of acetone-insoluble material was removed (Frac-