to plasma concentration ratio can be approximated by Eq. 6 during the entire study period.

Comparison of Eq. 7 with the definition of apparent clearance, K_{app}, given by Eq. 2 yields:

$$K_{app} = \frac{QK}{Q + K} \qquad \text{(Eq. 8)}$$

and:

$$K = \frac{QK_{app}}{Q - K_{app}} \qquad \text{(Eq. 9)}$$

These equations apply to all organs except the lung where all the venous blood from all organs converges. A similar derivation for the lung gives:

$$(K_{app})_{lung} = K_{lung}(Q_{plasma} + K_{plasma})/Q_{plasma} \qquad \text{(Eq. 10)}$$

and:

$$K_{lung} = \frac{(Q_{plasma})(K_{app})_{lung}}{Q_{plasma} + K_{plasma}} \qquad \text{(Eq. 11)}$$

The reason for the difference is based on the definition of K_{app}; K_{app} is defined as the blood (or plasma) volume from which drug is completely removed in a unit time. For the other organs, the blood flows from the pooled plasma compartment into each individual organ. For the lung, the blood exits from the lung compartment into the plasma pool.

RESULTS AND DISCUSSION

Equation 8 shows that, as Q increases and approaches infinity, K_{app} approaches K. It is clear, then, that K is the true capacity of the organ to eliminate the drug. In other words, K is the intrinsic clearance, a concept developed for hepatic drug clearance (3). In fact, Eq. 8 reduces to the equation for hepatic clearance but is more general and applicable to all drug-eliminating organs except the lung.

In view of Eq. 8, which can be rewritten as:

$$K_{app} = K\left(1 - \frac{K}{Q + K}\right) = Q\left(1 - \frac{Q}{Q + K}\right) \qquad \text{(Eq. 12)}$$

the apparent clearance K_{app} is always smaller than K or Q. However, there will be no upper limit for the intrinsic clearance K. Once the value

of K_{app} is obtained from experiment using Eq. 2, K can be calculated from Eq. 9 by using the blood flow rate Q through that particular organ.

The alternative to this approach is to rearrange Eq. 12 to yield:

$$K = \frac{K_{app}}{1 - E} \qquad \text{(Eq. 13)}$$

where:

$$E = \frac{K}{Q + K} = \frac{K_{app}}{Q} \qquad \text{(Eq. 14)}$$

is the steady-state extraction ratio, defined as the amount of drug eliminated divided by the amount of drug entering the organ at steady state. The approximation of K by K_{app} is valid only when the extraction ratio E is very small ($E < 0.05$). Most anticancer drugs have small E values, and this approximation is reasonable. However, when E is high and closer to unity, serious error of as much as an order-of-magnitude difference in K and as much as 50% in the estimated E may result from the approximation of K by K_{app}. Therefore, for drugs that have high hepatic extraction ratios such as doxorubicin ($E = 0.6$) (1), fluorodeoxyuridine ($E = 0.95 \sim 0.98$) (4), and fluorouracil [$E = 0.9$ in one study (5) and $E = 0.2$–0.5 in another (4)], Eq. 9 or 13 always should be used to calculate the intrinsic clearance.

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COMMUNICATIONS

New Calculation Method for Mean Apparent Drug Volume of Distribution and Application to Rational Dosage Regimens

Keyphrases □ Drug distribution volume—calculations, arithmetic mean method, harmonic mean method □ Dosage regimens—design, calculation of drug distribution volume, arithmetic mean method, harmonic mean method

To the Editor:

One important purpose of clinical pharmacokinetic studies is to obtain mean pharmacokinetic data to be used as an initial guide for drug therapy. The apparent volume of distribution (V_d) of a drug is a useful pharmacokinetic parameter in the one-compartment open-model system, which is often adequate clinically for the characterization of drug disposition kinetics (1–5). For example, the product of the mean V_d ($\overline{V}_d$) obtained from several subjects and

the desired plasma level ($\overline{C}_p$) of the drug could be equal theoretically to the *mean* priming dose recommended for the same type of patient.

The mean V_d of test subjects has been calculated almost exclusively to date by the arithmetic mean method. In this method, the individual V_d values (V_{d1}, V_{d2}, ..., V_{dn}) estimated by various standard or approximate (3) methods are added and the sum is divided by the total number of test subjects (n). The purposes of this communication are to propose a new method for calculating the mean V_d and to point out the potential shortcoming of the conventional arithmetic mean method in predicting rational dosage regimens.

If the test subjects are representative of the mean patient population, one should expect that the recommended mean dose ($\overline{V}_d\overline{C}_p$) when applied to the original test subjects should *ideally* result in an arithmetic mean plasma level of all the test subjects *exactly* equal to the originally targeted $\overline{C}_p$ value. In other words:

Table I—Reported Apparent Volumes of Distribution of Gentamicin in 11 Patients and Simulated Initial Serum Gentamicin Levels after Intravenous Bolus Doses Calculated Based on the Arithmetic and Harmonic Mean Methods for the Calculation of Mean Volume of Distribution and Initial Mean Targeted Level of 10 mg/liter

Patient	V_d, liter/kg	$C_{p(ari)}$, mg/liter	$C_{p(har)}$, mg/liter
1	0.19	12.94	12.11
2	0.19	12.94	12.11
3	0.22	11.18	10.45
4	0.25	9.84	9.20
5	0.20	12.30	11.50
6	0.29	8.48	7.93
7	0.20	12.30	11.50
8	0.49	5.02	4.69
9	0.22	11.18	10.45
10	0.25	9.84	9.20
11	0.21	11.71	10.95
Arithmetic mean	0.246	10.70	10.00

Table II—Reported Apparent Volumes of the Central Compartment of Theophylline in Nine Cirrhotic Patients and Simulated Initial Plasma Theophylline Levels after Intravenous Bolus Doses Calculated Based on Arithmetic and Harmonic Mean Methods for the Calculation of the Mean Central Compartment Volume and Initial Mean Targeted Level of 10 mg/liter

Patient	V_p, liter/kg	$C_{p(ari)}$, mg/liter	$C_{p(har)}$, mg/liter
1	0.448	7.37	4.44
2	0.144	22.92	13.82
3	0.781	4.23	2.55
4	0.095	34.74	20.95
5	0.157	21.02	12.68
6	0.163	20.25	12.21
7	0.146	22.60	13.63
8	0.282	11.70	7.06
9	0.753	4.38	2.64
Arithmetic mean	0.330	16.58	10.00

$$\overline{C}_p = (C_{p1} + C_{p2} + \ldots + C_{pn})/n \qquad \text{(Eq. 1)}$$

where C_{p1}, C_{p2}, ..., C_{pn} are the resultant individual plasma levels for the n subjects, respectively. Since:

$$C_{pi} = \frac{\text{dose}}{V_{di}} = \frac{\overline{V}_d \overline{C}_p}{V_{di}} \qquad \text{(Eq. 2)}$$

combination of Eqs. 1 and 2 would result in:

$$\frac{1}{\overline{V}_d} = \frac{1}{n}\left(\frac{1}{V_{d1}} + \frac{1}{V_{d2}} + \ldots + \frac{1}{V_{dn}}\right) \qquad \text{(Eq. 3)}$$

This equation clearly shows that for the purpose of predicting a *correct* mean dosage, the mean V_d must be calculated by Eq. 3, which is commonly referred to as the harmonic mean method.

When different doses are used on the test subjects, Eq. 3 becomes:

$$\frac{1}{\overline{V}_d} = \frac{1}{n}\left(\frac{C'_{p1}}{\text{dose}_1} + \frac{C'_{p2}}{\text{dose}_2} + \ldots + \frac{C'_{pn}}{\text{dose}_n}\right) \qquad \text{(Eq. 4)}$$

where C'_{p1}, C'_{p2}, ..., C'_{pn} are the resulting plasma levels for the n subjects, respectively. The plasma level from each subject can be corrected further based on the same total dose or some dose per unit of body weight or body surface area:

$$\frac{1}{\overline{V}_d} = \frac{1}{(n)(\text{dose})}(C''_{p1} + C''_{p2} + \ldots + C''_{pn}) \qquad \text{(Eq. 5)}$$

Therefore:

$$\overline{V}_d = \frac{\text{dose}}{(C''_{p1} + C''_{p2} + \ldots + C''_{pn})/n} \qquad \text{(Eq. 6)}$$

$$\overline{V}_d = \frac{\text{dose}}{\text{arithmetic mean plasma level}} \qquad \text{(Eq. 7)}$$

In other words, the mean V_d can be calculated also by dividing the dose (corrected to the same amount for all of the test subjects) by the arithmetic mean plasma level of the test subjects. This method will be referred to as the arithmetic mean–plasma level method. Obviously, these analyses can be applied equally well to the calculation of the mean apparent volume of the central compartment or the mean initial apparent volume of drug distribution in the multicompartment open model or the polyexponential plasma level decay system.

Literature examples on gentamicin, theophylline, and propranolol will be used to illustrate the differences in the mean volume of distribution and the initial plasma level that might result from the use of the two different methods for the volume of distribution calculation.

The data on the apparent volume of distribution of gentamicin in 11 burn patients (Table I) were reported by Sawchuk and Zaske (6). Their mean V_d based on the arithmetic mean method was 0.246 liter/kg. The mean V_d will be reduced to 0.230 liter/kg if the harmonic mean method is used. The data on the apparent volume of the central compartment (V_p) of theophylline in nine cirrhotic patients (Table II) were taken from a study of Piafsky *et al.* (7). The mean V_p reported, based on the arithmetic mean method, was 0.330 liter/kg. Based on the harmonic mean method, the mean V_p is 0.199 liter/kg. The arithmetic mean V_p of propranolol in three normal subjects was reported by Gomeni *et al.* (8) as 0.867 liter/kg. The mean V_p is, however, only 0.591 liter/kg based on the harmonic mean method. Different methods for calculating the mean V_d or V_p for these three drugs produce discrepancies ranging from 6.96 to 65.8% (Table III).

If the mean doses based on the two methods to achieve a mean serum or plasma level of 10 mg/liter for gentamicin or theophylline were used in these same patients, variations in the same manner in both individual or mean arithmetic mean serum or plasma levels would result (Tables I and II).

Although the arithmetic mean method for the mean volume of distribution calculation appears to be mathematically correct and the information obtained is useful, the harmonic mean or arithmetic mean–plasma level method reported here is the superior or perhaps the only correct method when the mean volume of distribution data

Table III—Summary of the Mean Apparent Volume of Distribution of Gentamicin and Mean Volumes of the Central Compartment of Theophylline and Propranolol in Human Subjects Estimated by Arithmetic and Harmonic Mean Methods

Method	Gentamicin, liter/kg	Theophylline, liter/kg	Propranolol, liter/kg
Arithmetic mean	0.246	0.330	0.867
Harmonic mean	0.230	0.199	0.591
Percent difference based on harmonic mean method as a reference	6.96	65.8	46.7

from the clinical trial are intended for designing a rational dosage regimen. The mean volume of distribution calculated from the test subjects should accurately predict their own plasma levels, even if the information is not intended for designing a rational dosage regimen.

In some studies, all individual plasma or serum data from the test subjects were grouped together and the pharmacokinetic analysis was performed based on these arithmetical *averaged* plasma or serum data (9). In intravenous bolus studies, the calculated mean initial volume of distribution obviously will be identical to the value calculated by the harmonic mean method and different from that calculated by the arithmetic mean method. This fact, which has probably not been pointed out before, might contribute to the difference in values reported from different studies.

In an earlier study (10) on clinical theophylline pharmacokinetics, the investigators reported that, depending on the methods used to calculate the mean total body clearance, as much as a 25–30% difference in the recommended infusion rate could occur. This phenomenon was considered as "unfortunate" (10). This author has made a similar analysis as presented in this communication and concluded that the best method for calculating the mean total body clearance in designing a rational dosage regimen is the harmonic mean method. Details of analyses will be reported later.

The preceding discussion is based on the assumption that the arithmetic mean method be used for the calculation of the mean plasma level. This approach was justified because the arithmetic mean method has been used almost exclusively for averaging peak, trough, steady-state, or mean steady-state plasma levels of drugs or metabolites in pharmacokinetic studies. This is probably also the case with mean levels of endogenous substances such as creatinine and urea reported in the literature. Statistically speaking, if the geometric, harmonic, or other mean method can be shown to be the best method for averaging plasma level data, then a different conclusion regarding the proper method for averaging the apparent volume of distribution can be obtained. The method proposed here can be applied to the calculation of other mean volumes of distribution such as the distribution volume at steady state.

In estimating the apparent volume of distribution of drugs after oral administration, the potential hepatic and pulmonary first-pass effects are often ignored. Appropriate equations are available for correcting for such effects (11–13). The harmonic mean method has been recommended for the calculation of the mean biological half-life of drugs (14).

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Prostaglandin Prodrugs IV: Empirical Relationship between Functional Group Contributions and Melting Points of C₁-Esters
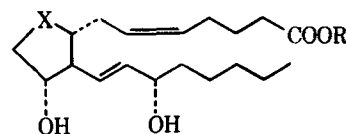
To the Editor:

Many prostaglandins occur as viscous liquids at room temperature, which presents problems in various pharmaceutical processes such as weighing and formulation. We recently showed that certain crystalline esters of the E-series prostaglandins are remarkably more stable than the parent prostaglandins (1). Now, based on melting-point data of numerous dinoprostone (I) and dinoprost (II) C₁-esters accumulated in our laboratories, we present a functional group contribution analysis of the influence of structure on melting points.
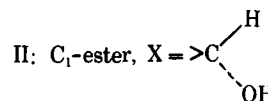
In principle, the melting point (T_m) of a substance can be calculated from:

$$T_m = \frac{\Delta H_f}{\Delta S_f} \qquad \text{(Eq. 1)}$$

where ΔH_f and ΔS_f are the heat and the entropy of fusion,

I: C₁-ester, $X = {>}C{=}O$

II: C₁-ester, $X = {>}C{<}^H_{OH}$