Table II—Sulfamethizole Clearance Rate (liters/24 hr)

Dog	Constant Infusion Method	Constant Withdrawal Method
1	2.0	2.1
2	2.9	2.9
3	1.9	1.8
4	1.5	1.5
5	2.1	2.5

The plasma concentrations of sulfamethizole that were registered during these three tests in one dog are shown in Fig. 1. Although the plateau level of sulfamethizole was different in each experiment, the calculated clearance rates were essentially equal. The results in all of the dogs are given in Table I. As can be seen, the clearance rate remained unaffected by changes in the sulfamethizole concentration.

After the clearance rate of sulfamethizole was measured by the constant infusion method, each dog was restudied by the single intravenous injection method. After a pulse injection of sulfamethizole, the level of sulfamethizole in the blood was followed by multiple blood withdrawals from one limb and a continuous constant withdrawal from another limb. A representation of the disappearance curve for one dog is given in Fig. 2.

The results obtained by the two methods are given in Table II. There was no significant difference between the clearance rates obtained ($p < 0.001$ by the paired t test).

The initial peak concentration of the drug, which occurs a short time after the pulse intravenous injection, has a major effect on the final integral, but there is no way to predict the initial integral from the instant of injection to the first blood sampling. This problem is solved by the continuous constant withdrawal, since $\Delta t \rightarrow 0$ in this method. The integral of the concentration curve from the first moment of sampling (t = 15 min) was calculated by the trapezoidal rule. The difference between the two integrals allows the calculation of the initial integral ($\int_0^{15} X' dt$) and the initial IC_{15}.

In the five described experiments, IC_{15} was always higher than the extrapolated concentration at $t = 0$ calculated by the semilogarithmic linear regression (Table III). The accuracy of the constant blood-withdrawal method was demonstrated by the similarity between the clearance rate obtained by the two methods.

Table III—Calculated Initial Concentration of Sulfamethizole

Dog	Extrapolation to $t = 0$, mg/liter	IC_{15}, mg/liter
1	37.8	278.6
2	31.2	161.9
3	56.7	250
4	60.3	365.1
5	37.0	232.6

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Volume of Distribution as a Function of Time

SARFARAZ NIAZI

Abstract □ A single definition for all volume terms in pharmacokinetic modeling is proposed; this parameter is considered as a function of time. This definition will represent the kinetic nature of pharmacokinetic models and will provide a highly sensitive parameter for correlation with pharmacological responses.

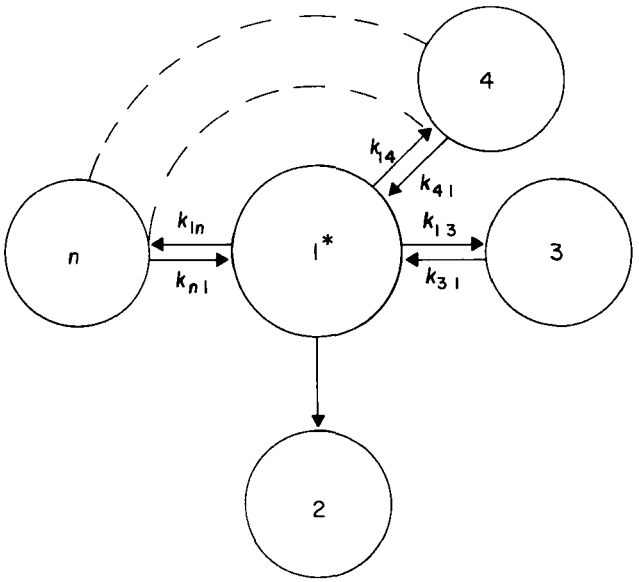
Keyphrases □ Volume—terms in pharmacokinetic modeling, single definition proposed as a function of time □ Pharmacokinetic modeling—single definition for all volume terms proposed as a function of time □ Distribution volume—volume terms in pharmacokinetic modeling, single definition proposed as a function of time

In the pharmacokinetic modeling of the absorption, distribution, metabolism, and excretion of drugs, various volume terms have been defined, such as the volumes of central (V_c) and tissue (V_T) compartments, the steady-state volume of distribution ($V_{d_{ss}}$), and the volume of distribution following pseudo-distribution equilibrium (V_{d_β} or $V_{d_{area}}$) (1–9).

The purpose of this paper is to propose a single definition for volume terms that can be used regardless of the complexity of the pharmacokinetic model. If this term is considered as a variable rather than a constant, this parameter will be more meaningful and add a new dimension to the characterization of drug response through pharmacokinetic studies.

THEORETICAL

When a drug is introduced in the body such as by intravenous injection, it starts to eliminate and to distribute to other parts of the body instantaneously (Scheme I). The measured concentra-



Scheme I—Mammalian system with n *compartments. The* (*) = *central, sampled compartment.*

tion, C_1, can be expressed as:

$$C_1 = \sum_{i=1}^{n} A_i e^{-a_i t} \qquad \text{(Eq. 1)}$$

where A_i is the intercept on the C_1 *versus* time plot, and a_i is the hybrid rate constant.

The total area under the C_1 *versus* time plot (AUC_∞) is proportional to the dose made available to the body (D_A) regardless of the route of administration (6):

$$D_A \alpha AUC_\infty = \int_0^\infty \sum_{i=1}^{n} A_i e^{-a_i t} = \sum_{i=1}^{n} \frac{A_i}{a_i} \qquad \text{(Eq. 2)}$$

In a multicompartment model where the drug is eliminated only from the central compartment, the amount of drug remaining in the body (D_B) as a function of time can be expressed in terms of fractional area (10):

$$D_B = \frac{D_A \int_t^\infty \sum_{i=1}^{n} A_i e^{-a_i t}}{\sum_{i=1}^{n} \frac{A_i}{a_i}} = \frac{D_A \sum_{i=1}^{n} \frac{A_i e^{-a_i t}}{a_i}}{\sum_{i=1}^{n} \frac{A_i}{a_i}} \qquad \text{(Eq. 3)}$$

The term volume of distribution is expressed as the ratio of the amount of drug in body and the measured concentration:

$$V_d = \frac{D_B}{C_1} = \frac{D_A \sum_{i=1}^{n} \frac{A_i e^{-a_i t}}{a_i}}{\sum_{i=1}^{n} \frac{A_i}{a_i} \sum_{i=1}^{n} A_i e^{-a_i t}} \qquad \text{(Eq. 4)}$$

This equation can be used for all compartmental models, linear or nonlinear, and provides one definition of volume of distribution as a function of time. At time $t = 0$, the volume of distribution becomes:

$$V_{d_0} = \frac{D_A}{\sum_{i=1}^{n} A_i} \qquad \text{(Eq. 5)}$$

This is analogous to the volume of the central compartment. Similarly, as time exceeds some value, t^* (*i.e.*, attainment of pseudo-distribution equilibrium):

$$\sum_{i=1}^{n} A_i e^{-a_i t^*} \simeq A_n e^{-a_n t^*} \qquad \text{(Eq. 6)}$$

the volume of distribution becomes constant and is referred to as the volume of distribution following pseudo-distribution equilibrium:

$$V_{d_{eq}} = \frac{D_A}{a_n \sum_{i=1}^{n} \frac{A_i}{a_i}} \qquad \text{(Eq. 7)}$$

This equation is the same as was described by Perrier and Gibaldi (9) except for the term D_A, which is the available dose compared to the intravenously administered dose. In some instances, these two may not be the same. For example, compounds mainly eliminated through the lungs undergo a first-pass effect if the compound is administered intravenously (11, 12).

The rate at which the volume of distribution V_{d_0} approaches $V_{d_{eq}}$ represents the distribution nature of the drug. Differentiation of Eq. 4 leads to:

$$\frac{dV_d}{dt} \simeq \frac{D_A \left[\sum_{i=1}^{n} \frac{A_i e^{-a_i t}}{a_i} \sum_{i=1}^{n} a_i A_i e^{-a_i t} - \left(\sum_{i=1}^{n} A_i e^{-a_i t} \right)^2 \right]}{\left[\left(\sum_{i=1}^{n} A_i e^{-a_i t} \right)^2 \sum_{i=1}^{n} \frac{A_i}{a_i} \right]} \qquad \text{(Eq. 8)}$$

An important parameter can be the rate of volume of distribution change at $t = 0$, RV_{d_0}, and from Eq. 8:

$$RV_{d_0} = \frac{dV_d}{dt} \text{ (at } t = 0) = \frac{D_A \sum_{i=1}^{n} a_i A_i}{\left(\sum_{i=1}^{n} A_i \right)^2} - \frac{D_A}{\sum_{i=1}^{n} \frac{A_i}{a_i}} \qquad \text{(Eq. 9)}$$

This parameter will most characteristically describe the distributional behavior of drugs in the body since it is not only the function of $V_{d_{eq}}$ but also of the rate at which it is achieved. It will be shown later that this is a highly sensitive index to intersubject and intrasubject variations in the distributional properties of a drug and an important parameter for correlation between the drug responses based on the rate at which the site of action is saturated.

DISCUSSION

The pharmacokinetic parameter of volume has several connotations (7) and is generally used to describe an actual size of the body region (8), such as the volume of body fluid dissolving the substance at the same concentration as the plasma (13), or the volume of a particular compartment assuming that all of the substance or drug concentration within the compartment is actually distributed at a uniform concentration equal to the concentration measured in a particular reference region (2). The confusion in defining and expressing the volume terms often has resulted due to the misrepresentation of the essential characteristics of compartmental modeling.

First, the compartment model for the disposition of a drug is a kinetic representation characterizing the absorption, distribution, and elimination properties. Consequently, these interpretations should be limited to the rate processes expressed as compartments, which may have little physical meaning as discrete units. Therefore, it is not justified to categorize a group of tissues as representing a compartment (6). For example, a drug acting on the myocardium often is erroneously classified as having its site of action in the central compartment whereas it may actually be a part of another compartment, depending on the rate at which it undergoes equilibration.

Second, the equilibration between the site of administration and other parts of the body is a function of the thermodynamic activity

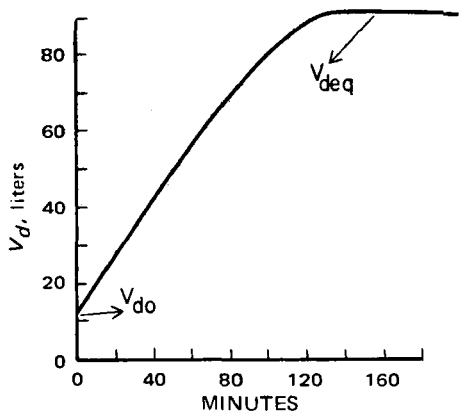


Figure 1—*Volume of distribution of trichloromonofluoromethane as a function of time following intravenous administration in a dog.*

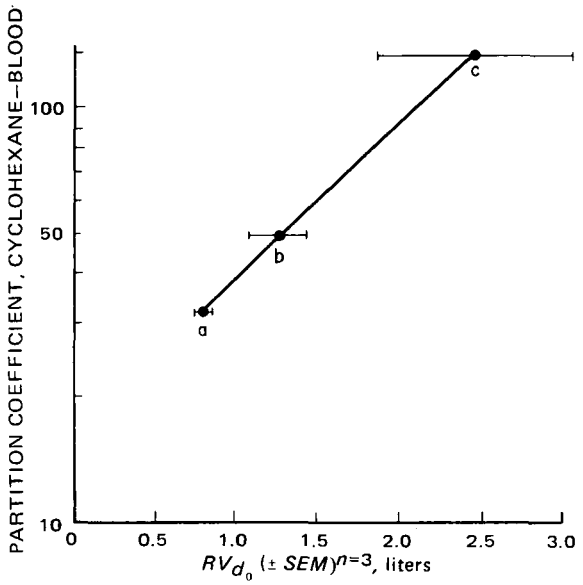


Figure 2—*Initial rate of volume of distribution change as a function of partition coefficient. Key: a, trichloromonofluoromethane; b, dichlorodifluoromethane; and c, dichlorotetrafluoroethane.*

of the drug. Therefore, such terms as volume and concentration of tissue compartments have little meaning. Briefly, the kinetics of absorption, distribution, and elimination of drugs should be viewed as continuous rate processes represented by compartments that undergo equilibration to yield uniform thermodynamic activity in the body.

In terms of continuous rate processes, when a drug is introduced in an easily accessible fluid or tissue of the body, the processes of distribution and elimination begin simultaneously, resulting in a nonproportional relationship between the amount of drug in the body and the concentration measured in any specific part of the body. This proportionality can be expressed by the term volume which, as a function of time, should characterize the distributional nature of the drug in the body.

This new perspective in the definition of the volume of distribution will make this parameter more useful in the characterization of drug response and drug properties in general. For example, drugs having low solubility in the blood should be expected to show a greater RV_{d_0}, rate of volume change at $t = 0$, compared to highly soluble compounds simply because of their higher chemical potential if the nonprotein bound or, more appropriately, the activity is measured in the blood. A higher value of RV_{d_0} may be expected if the drug molecules have higher affinity for the tissues with which they are equilibrating. Since RV_{d_0} is also proportional to $V_{d_{eq}}$, it not only represents the affinity for distribution but also the capacity.

It has been suggested that the biological activity of many drugs depends on the rate at which they interact with the receptor site (14), and this can be characterized easily by comparing RV_{d_0} for a series of drugs and their potency. Therefore, this term can be employed in the characterization of the drug–receptor interaction.

The concept of the volume of distribution as a function of time is depicted in Fig. 1, which illustrates the data for trichloromonofluoromethane calculated from pharmacokinetic parameters reported recently (11, 12). A further evaluation of these data shows that the term RV_{d_0} for three fluorocarbon aerosol propellants can be correlated to several *in vitro* properties (11, 12).

For example, Fig. 2 shows the relationship between RV_{d_0} and the partition coefficient between cyclohexane and blood. A log–linear relationship shows that dichlorotetrafluoroethane equilibrates much faster with tissues that are lipoidal in nature since cyclohexane often has been shown to mimic the fatty tissue properties (15).

However, this comparison of RV_{d_0} and partition coefficients is made based on whole blood concentration measurements, and this relationship might change if due consideration is given to thermodynamic activity in the blood rather than concentration.

The term RV_{d_0} thus provides more information than can be obtained from the consideration of the volume of distribution itself. For example, if the following blood concentration profiles are obtained for a drug in two subjects:

$$C_1 = 80e^{-0.0693t} + 20e^{-0.01386t} \text{ (Subject 1)} \qquad \text{(Eq. 10)}$$

$$C_1 = 85e^{-0.0561t} + 15e^{-0.01386t} \text{ (Subject 2)} \qquad \text{(Eq. 11)}$$

they give identical values for the volume of distribution at equilibrium (13.88 liters), the volume of distribution at $t = 0$ (5 liters), the terminal disposition half-life (50 min), and AUC_∞ (2597.40 μg min/ml). However, the RV_{d_0} values differ by 75% (Subject 1 = 98.56 ml/min; Subject 2 = 56.32 ml/min). Such a difference may be important for drugs whose action depends on the rate of equilibration. Thus, the RV_{d_0} can be better correlated with various pharmacological, physiological, and toxicological parameters.

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