Volume Terms in Pharmacokinetics

Keyphrases ☐ Volume terms—pharmacokinetic definitions ☐ Distribution volume terms—comparison ☐ Steady-state distribution terms—use, limitations

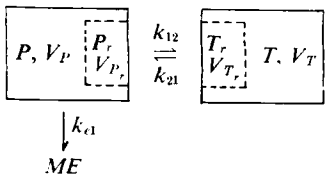
Sir:

Volume terms, designated by a V, are used in pharmacokinetics and biopharmaceutics for three purposes. First, a volume constant might be used to describe the actual size of a body region as recently used in describing thiopental pharmacokinetics (1). Under these conditions the value of V is given some physiological meaning. The second use for the term V is as a volume of distribution. The concept of the volume of distribution was introduced by Dominguez (2) and was defined by him as the hypothetical "volume of body fluid dissolving the substance at the same concentration as the plasma." Presently the volume of distribution is taken to refer to the volume of a particular compartment if we were to assume that all of the substance or drug contained within the compartment were actually distributed at a uniform concentration which is equal to that concentration measured in a particular reference region (3). Although the volume of distribution may not have any implication as to the actual distribution of the substance, it is a valuable constant which allows one to calculate the total amount of substance or drug in a compartment, if one is able to measure the concentration in a reference region such as the plasma.

The third use of the term V is employed with reference to the volume of an unsampled compartment. This use of V may be restricted to describing a volume or volume of distribution for a single compartment within a model, such as V_T in Model I, or it may be used to describe a summed volume or a volume of distribution for a number of compartments, at least one of which has not been sampled. Riggs (3) has introduced the use of an overall volume of distribution term, and has labeled it the volume of distribution steady state ($V_{d_{ss}}$). This volume term is defined specifically with respect to the two-compartment open model (see Model I). The volume of distribution steady state equals the total quantity of drug in the body divided by the concentration in the reference region of the central compartment, these measurements taken at the time when the tissue compartment contains the maximum amount of drug (see Eq. 1). The purpose of this communication is to define the conditions where the terms $V_{d_{ss}}$ and V_T may be useful in the pharmacokinetic analysis.

The two-compartmental open system (Model I) will be defined using the terminology of Riegelman *et al.* (6), with the additional schematic representation of reference regions within each compartment.

Model I clearly indicates that within the kinetic description utilized, the central compartment includes those portions of the intercellular fluids and tissues which appear to come into equilibrium with the blood



Model I

where:

- T = the amount of drug in the tissue (peripheral) compartment (including the reference region) at any time, t.
- P = the amount of the drug in the central compartment (including the reference region) at time, t.
- ME = the amount of drug eliminated by all processes of metabolism and excretion, assumed to take place exclusively in the central compartment, up to time, t.
- V_P, V_T = the volumes of distribution (as defined above) of the central and tissue compartments, respectively.
- P_r = the amount of drug in the reference region of the central compartment at time, t.
- T_r = the amount of drug in an assumed reference region of the tissue compartment at time, t.
- V_{Pr} = the actual volume of the reference region in the central compartment. This volume has a physiological significance as defined above.
- V_{Tr} = the volume of the hypothesized reference region in the tissue compartment. This would be the actual volume in the tissue compartment, throughout which the concentration of the reference region is constant.
- k_{12}, k_{21} = first-order rate constants of distribution.
- k_{el} = the sum of the simultaneous processes of metabolism and excretion all assumed to be first-order.
- $'$ = primed terms indicate amounts or concentrations taken at the time when the amount of drug in the tissue compartment is at a maximum.
- C = concentrations.

instantaneously. The volume of distribution steady state as defined above may be expressed as:

$$V_{d_{ss}} = \frac{(P' + T')}{C_{Pr}'} \qquad \text{(Eq. 1)}$$

Equation 1 is only the definition of $V_{d_{ss}}$. The equation, however, gives us no useful information about a drug and its distribution within the body. Therefore, it is necessary to understand how $V_{d_{ss}}$ is related to other pharmacokinetic parameters. The volume of distribution steady state is derived in the following manner. When the amount of drug in the tissue compartment reaches a maximum, the rate of transfer from the central to the tissue compartment must be exactly equal to the rate of transfer from the tissue to the central compartment as shown in Eq. 2.

$$k_{12}P' = k_{21}T' \qquad \text{(Eq. 2)}$$

Substituting volumes of distribution and reference compartment concentrations for amount terms, Eq. 2 becomes:

$$k_{12}V_P\, C_{Pr}' = k_{21}V_T C_{Tr}' \qquad \text{(Eq. 3)}$$

Rearranging Eq. 3 and realizing that the ratio of concentrations in the reference compartments at time t' equals the ratio of concentrations we would expect to find at equilibrium for a two-compartment closed model, we may substitute the partition coefficient for

the drug between these two reference compartments

$$R_{T/P} = \frac{C_{Tr}'}{C_{Pr}'} \qquad \text{(Eq. 4)}$$

into Eq. 3 with the following result:

$$V_T R_{T/P} = \frac{k_{12}}{k_{21}} V_P = \frac{T'}{C_{Pr}'} = (V_{\text{dist.}})_{T/P} \qquad \text{(Eq. 5)}$$

Equation 5 defines what Riggs (3) calls the volume of distribution in the tissue compartment with respect to the concentration in the reference region of the central compartment, $(V_{\text{dist.}})_{T/P}$. It should be noted that this volume of distribution is a function of the partition coefficient between the reference region of each compartment and not the partition coefficient between the two compartments. In the above equations, the inclusion of a reference region in the tissue compartment is not a necessary assumption in the derivation. If no reference region is hypothesized, $R_{T/P}$ becomes the partition coefficient between the entire tissue compartment and the reference region of the central compartment.

From Eqs. 1 and 5, and the definition of V_P, the volume of distribution steady state may also be described by Eq. 6.

$$V_{d_{ss}} = V_P + V_T R_{T/P} = V_P + (V_{\text{dist.}})_{T/P} = \left(1 + \frac{k_{12}}{k_{21}}\right) V_P \qquad \text{(Eq. 6)}$$

Use of the Volume of Distribution Steady State—The question now arises as to what use can the volume of distribution steady state be put? Gibaldi *et al.* (4) have clearly shown that the volume of distribution steady state will not serve the usual function of a volume of distribution, that is, to relate measured concentrations to the known amounts of drug in the body throughout the time course of the drug in the body. Riegelman *et al.* (5, 6) have presented an excellent argument for utilization in pharmacokinetics of the two-compartment model as opposed to the single-compartment concept. They point out that there is a large variance between the volumes of distribution for acetylsalicylic acid and salicylic acid if these drugs are described only by a single-compartment model. They then go on to point out that when a two-compartment model is used to describe the pharmacokinetics of these two drugs, the respective calculated volumes of distribution, V_P and $V_{d_{ss}}$, are very close as would be expected for two such structurally similar drugs (6, 7). We would like to emphasize that it is not the similarity between $V_{d_{ss}}$ which confirms their expectation of similar distribution for the two drugs, but rather the identity between the volume of distribution of the central compartment for each of these drugs *and* the identity between the ratio of distribution rate constants for these drugs. That is, it would be possible for two drugs to have identical volumes of distribution steady state and still have widely differing volumes of distribution for the central compartment. In this latter case it would be erroneous to assume that the two drugs distributed similarly in the body just because we could calculate identical values for $V_{d_{ss}}$.

Riggs (3) discusses a number of "biased" methods for estimating the volume of distribution and points out that there seems to be "little justification for regarding volumes so calculated as equivalent to *true* volumes of distribution. . . ." (emphasis added). Riegelman *et al.* (6) correctly point out that all of the "biased" estimates for the volume of distribution are dependent on rate constants for elimination, and there is certainly no justification for a volume of distribution to be dependent on the rate of elimination. However, the "true" volume of distribution ($V_{d_{ss}}$) seems to have little use. It cannot relate measured concentrations to amounts of drug in the body and it cannot be used in any physiological interpretation in the two-compartment model unless its component parts (previously calculated) are also compared. In fact, when $V_{d_{ss}}$ is used to compare intersubject variation for a single drug or to compare the distribution of similar drugs within a subject, it has the disadvantage of obscuring the difference or similarities since $V_{d_{ss}}$ is a function of the sum of two variables, both of which could vary independently.

Gibaldi (14) has shown that under conditions of steady state, as in zero-order infusion, $V_{d_{ss}}$ may be calculated without the necessity of establishing the appropriate model or determining the distribution and elimination rate constants. Thus $V_{d_{ss}}$ may serve a unique function as a parameter for comparing drug distribution when the distribution and elimination rate constants cannot be determined. However under these conditions the investigator should be aware of the limited value of $V_{d_{ss}}$ and that $V_{d_{ss}}$ is only partially model independent. We have said "partially" independent since $V_{d_{ss}}$ was defined as a volume parameter independent of elimination processes. This is only true if elimination processes occur exclusively in the central compartment. For example, if some type of metabolism or elimination took place in the tissue compartment of the two-compartment model (this rate described by the constant k_{24}) the volume of distribution steady state would be a function of this elimination rate constant as shown in Eq. 7:

$$V_{d_{ss}} = V_P(1 + T'/P') = V_P\left(1 + \frac{k_{12}}{k_{21} + k_{24}}\right) \qquad \text{(Eq. 7)}$$

Use of V_T—The volume of distribution of the tissue compartment has been used with different connotations. For one interpretation Eq. 6 presents an appealing simplification. Since $R_{T/P}$ is the partition coefficient between the reference regions in the two compartments and not between the compartments as a whole, one needs only to assume that the tissue compartment contains a region of fluid where the solubility of the drug is identical to its solubility in the measured reference region of the central compartment. Thus one assumes that the partition coefficient between the two reference regions is one. This seems to be the approach that Wagner *et al.* (8, 9) have used in two-compartment analysis, where V_T is always defined as equal to $V_P \times (k_{12}/k_{21})$. This assumption is also implicit in the work of Teorell (10), Gaudino (11), and Dominguez (12). Thus, these authors are calculating the volume of distribution of the tissue compartment (V_T) with reference to the physical-chemical properties of the reference region in the central compartment (usually the plasma).

However, when V_T is used to describe the distribution in the tissue compartment, there is a tacit assumption that within the limited physiological meaning of the two-compartment model, some reference region within the tissue compartment (or the entire tissue compartment) has the physical-chemical properties of the plasma reference region. This seems to imply that if protein binding or hydrolysis occurs in the plasma compartment, it will also occur to the same extent in the tissue compartment. However, these implications are only the result of describing the tissue compartment with reference to V_T, and are unnecessary if amounts are used to describe the time course of the drug in the tissue compartment.

Riegelman *et al.* (6) and Rowland *et al.* (13) have given the following definition for $V_{d_{ss}}$ with respect to the two-compartment open model:

$$V_{d_{ss}} = V_P + V_T = \left(1 + \frac{k_{12}}{k_{21}}\right) V_P \qquad \text{(Eq. 8)}$$

It would appear in comparing Eq. 8 with Eq. 6 that these authors are assuming that $R_{T/P}$ has a value of 1.0. However, they are in fact defining V_T as equivalent to Riggs' $(V_{\text{dist.}})_{T/P}$ as presented in Eq. 5 (15). This is not at all clear from their model (which is similar to the one presented in this paper with the exclusion of the reference regions) or from their definition of volume terms where V_P and V_T are described by a single definition: "the volumes of central and tissue compartment, respectively" (6). Although this definition is unclear, it does not affect the pharmacokinetic interpretion of the data. However, the inclusion of reported values for V_T and the assignment of volumes in liters to the tissue compartment offers the potential for a physiological interpretation of this volume, even though everyone is agreed that no physiological meaning should be attached to these volumes (2, 3, 5–13).

Use of Amount Terms—The two-compartment model may be described unambiguously without the use of V_T and $V_{d_{ss}}$. The rate constants determined from pharmacokinetic data are always "amount rate constants." That is, steady state or equilibrium is reached in Eq. 2 when the products of the *amount* of drug in a compartment and the "amount rate constant" are equal on both sides of the equation. Thus even though the concentrations are measured in the plasma reference region, the only general description of the model which is exact is the total amount of drug in each compartment at a particular instance. Since T, the amount of drug in the tissue compartment, may be calculated at any time, we do not see any advantage in defining a volume term so as to be able to calculate a hypothetical concentration. If a comparison of the distribution of a drug between the central and tissue compartments at any particular time is desired, both P and T may be calculated easily. If one is specifically interested in calculating T and P during the β-phase (where a plot of log plasma concentration *versus* time is linear) T and P are related by a constant, and the calculation of T becomes even easier (14, 16). If one wishes to know about the steady-state distribution of a drug, this is conveniently given by the ratio k_{12}/k_{21}. If the ratio is one, the drug distributes equally into both compartments. If the ratio is greater or less than one, the drug distributes preferentially into either the tissue or central compartment. If one wishes to compare the distribution of two different drugs within a single subject, one may compare V_P and the ratio k_{12}/k_{21}. Then only if both parameters are similar for the two drugs, may these drugs be assumed to be distributed similarly.

We do not mean to imply in this publication that because an author has used V_T or $V_{d_{ss}}$, he has therefore misinterpreted the pharmacokinetic data. However, we do not see the necessity of introducing a fictitious volume constant in order to describe a fictitious concentration. We feel that the time course of a drug can be adequately described by referring to the amount of drug in the tissue compartment and that the introduction of this third definition of volume into pharmacokinetics (volumes of compartments which cannot be sampled) and subsequent calculation of tissue "concentrations," offers only a great potential for the misinterpretation of the physiological distribution of drugs.

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