Distribution Volume Related to Body Weight and Protein Binding

Keyphrases □ Volume of distribution—related to body weight and protein binding □ Pharmacokinetics—distribution volume related to body weight and protein binding

To the Editor:

The physiological approach to drug distribution volume proposed by Gillette (1) has proven very useful for characterizing the dual effects of body size and plasma and tissue binding on steady-state volume of distribution (V_{ss}). Gillette's equation has commonly appeared as:

$$V_{ss} = V_p + \frac{f_{up}}{f_{ut}} V_t \qquad \text{(Eq. 1)}$$

where V_p is plasma volume, V_t is remaining body volume or mass accessible to drug, and f_{up} and f_{ut} are the fractions of unbound drug in plasma and tissues, respectively, which are assumed to be concentration-independent parameters.

Related conceptual models have been proposed by Wagner (2), Øie and Tozer (3), and others (reviewed in Ref. 4) with the assumptions that unbound drug diffusion serves as the equilibrating mechanism throughout body spaces, linear conditions exist, and the drug is bound and/or partitions into various tissue spaces. Equation 1 has been particularly helpful in pharmacokinetics as it rationalizes the meaning and calculation of V_{ss} as an essential "model-independent" parameter (5) and provides a means for estimating tissue binding of drugs. In the latter regard, Gibaldi and McNamara (6) revised Eq. 1 to yield a relationship which allowed calculation of f_{ut} based on assumption of reasonable values of V_p and V_t:

$$f_{ut} = \frac{V_t f_{up}}{V_{ss} - V_p} \qquad \text{(Eq. 2)}$$

The purpose of this communication is to further consider Eq. 1 in terms of the practice of normalizing V_{ss} for body weight and for f_{up}.

The adjustment of V_{ss} for total body weight (TBW) has been proposed as a means of expressing drug distribution in terms of an apparent tissue–plasma distribution or partition coefficient (5, 7):

$$K_D = V_{ss}/\text{TBW} \qquad \text{(Eq. 3)}$$

While further division of V_{ss}/TBW by f_{up} appears logical, the usefulness of the resulting parameter has not been ascertained. For oral dose clearance data, the analogous computation of Dose/f_{up} × AUC yields the intrinsic clearance of unbound drug, a parameter indicative of the V_{max}/K_m ratio for a biotransformation process (8, 9). It would be helpful if V_{ss}/f_{up} had a similar, direct physiological interpretation.

Equation 1 can be rearranged to the following expression upon division by f_{up} and substitution of TBW − V_t for V_p:

$$\frac{V_{ss}}{f_{up}} = \frac{\text{TBW}\, f_{ut} + V_t(f_{up} - f_{ut})}{f_{up} f_{ut}} \qquad \text{(Eq. 4)}$$

Since V_p is small compared to TBW, the approximation can be made that $V_t \simeq$ TBW and Eq. 4 simplifies and rearranges to:

$$K_D^u = V_{ss}\,\text{TBW}^{-1} f_{up}^{-1} = f_{ub}^{-1} \qquad \text{(Eq. 5)}$$

Thus, the calculation of V_{ss}, normalized both for body weight[1] and plasma binding, should yield a reasonable value for the reciprocal of f_{ub}, an estimate of the unbound fraction of drug in the body. This "intrinsic volume" should help in examining factors such as the effects of disease states on plasma and tissue binding of drugs.

While f_{ut} has been viewed (6) as "the average fraction of unbound drug in the extravascular water space weighted for tissue mass" according to Eq. 2, it serves in Eq. 5 as "the average fraction of unbound drug in the body weighted for tissue mass." Neither parameter can be considered more correct without direct quantitation of tissue binding. However, Eq. 5 is proposed for use because of several advantages. It obviates the need to estimate V_p and V_t in different persons or animals as body water spaces. The assumption that drugs are localized only in body water spaces is thereby removed, but the influences of lipid partitioning, active transport, ion trapping caused by pH differences among tissues, and binding to body solids become implicitly included (3, 4). As experimental capabilities for estimating tissue drug binding *in vitro* (4, 10) improve, the value of f_{ub} should prove easier to measure and calculate per unit of total tissue mass than per unit of tissue water.

One major value of Eq 5 is that calculation of K_D^u directly from free drug concentrations in plasma has been rationalized as having intrinsic merit. Equation 1 is difficult to employ when plasma protein binding is nonlinear. For prednisolone (which exhibits marked concentration-dependent binding to transcortin and albumin in plasma) the model-independent calculation of V_{ss} from plasma clearance (Cl) and mean transit time ($\bar{t}$):

$$V_{ss} = Cl\bar{t}/\text{TBW} \qquad \text{(Eq. 6)}$$

yields dose and time-average values of V_{ss} which vary with dose (11). Similar calculations can be made using free drug concentrations (C_u) and area–moment analysis (12) to yield:

$$K_D^u = \frac{\text{dose} \int_0^\infty t C_u dt}{\left(\int_0^\infty C_u dt\right)^2 \text{TBW}} = f_{ub}^{-1} \qquad \text{(Eq. 7)}$$

This approach served as the basis for comparing prednisolone pharmacokinetics in humans and rabbits. As shown in Fig. 1, both species yielded K_D^u values (time and dose average) which centered about 2 liters/kg. Extending the interpretation using Eqs. 5 and 7, the average body binding of the corticosteroid would be ~50%.

A second demonstration of the use of Eqs. 2 and 5 for estimation of drug binding is shown in Table I. Oxaprozin

[1] While K_D^u has units of liters/kg, it can be altered to a dimensionless number more equivalent to f_{ub}^{-1} by converting body weight to volume. Weight is retained here for simplicity.

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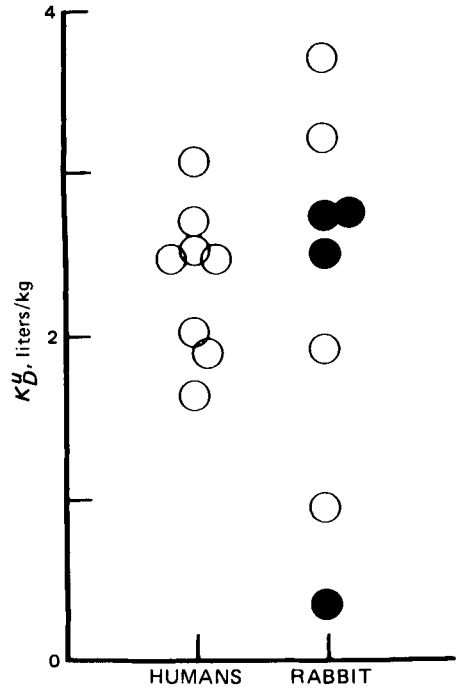

Figure 1—*Steady-state volume of distribution of unbound prednisolone calculated according to Eq. 7 for humans and rabbit.*

Table I—Protein Binding and Distribution Properties of Oxaprozin in Normal and Azotemic Subjects

Subjects	V_{ss}/TBW, liters/kg	f_{up}, %	K_D^u, liters/kg	f_{ut}, % Eq. 2[a]	f_{ub}, % Eq. 5
Normal	0.15 (0.01)	0.078 (0.003)	193 (11)	0.42 (0.03)	0.52 (0.03)
Renal impairment	0.18 (0.01)	0.177 (0.016)	103 (13)	0.79 (0.11)	1.03 (0.12)
Dialysis	0.21 (0.02)	0.283 (0.036)	79 (13)	1.05 (0.21)	1.43 (0.25)

[a] Assumes V_t = extravascular water space (554 ml/kg) and V_p = 46 ml/kg.

pharmacokinetics and binding were examined in subjects with normal and impaired renal function[2]. Direct plasma protein binding studies showed altered binding in plasma in the azotemic patients. The values of f_{ut} and f_{ub} were estimated by the two equations. The proposed equation did not obscure the apparent occurrence of impaired tissue binding in azotemic patients.

It is becoming common practice to calculate intrinsic clearance and the unbound volume of distribution directly from C_u *versus* time data. It is helpful to be able to interpret the resultant value in terms of overall drug binding. The necessary assumption that passive diffusion of unbound drug accounts for equilibration between tissues is retained. These arguments for simplified calculation of K_D^u, however, should not preclude the application of more specific tissue binding models when based on appropriate experimental data.

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[2] Unpublished data.

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Trace Decomposition of Choline

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To the Editor:

Decomposition of pharmaceuticals to the extent of parts per thousand, or less, usually is considered negligible. Such trace decomposition cannot be ignored where it affects the acceptability of drug products, *i.e.*, where it is manifested as insoluble matter in an injection, as discoloration, or by odor formation. The origin of a characteristic fishy odor in oxtriphylline (choline theophyllinate) exposed to high humidity for protracted periods or in unbuffered solutions led to the studies reported here. This odor, which is characteristic of many choline salts, can be attributed to trace decomposition; trace, because the presence of an odor has no measurable effect on physicochemical properties and decomposition, since quaternary ammonium salts are nonvolatile and would be expected to be odorless on that account.

A decomposition study of choline, measuring intact quaternary ammonium function, showed that it proceeded very slowly in solution at 100°. On heating choline has been reported (1) to yield 85–90% trimethylamine, 5% dimethylamine, 25% ethylene glycol, 4% acetaldehyde, and 10–15% acetylene on a molar basis with excess concentrated potassium hydroxide. The nature of the neutral reaction products would be expected to vary with reaction conditions, but it was assumed in this study that trimethylamine would constitute the bulk of the basic products. Because the amounts of trimethylamine formed were extremely low, a method was developed using microdiffusion to iso-

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