Table I—Equations for $\int_0^\infty X\,dt$ and $\int_0^\infty X\,dt$/Dose for Various Modes of Drug Administration

Mode of Administration	$\int_0^\infty X\,dt$	$\int_0^\infty X\,dt$/dose
Intravenous bolus	0	0
Intravenous infusion	$k_0T^2/2$[a]	$T/2$
First-order input	F dose/k_a[b]	$1/k_a$
Simultaneous bolus plus infusion	$k_0t^2/2$	$k_0T^2/2(k_0T + \text{dose}_{iv})$[c]
Two consecutive infusions	$(k_0T^2/2)_1 + (k_0T^2/2)_2$[d]	$\frac{(k_0T^2/2)_1 + (k_0T^2/2)_2}{(k_0T)_1 + (k_0T)_2}$[c]

[a] See Eqs. 4 and 6. [b] See Eqs. 5 and 7. [c] See Eq. 13. [d] Subscript 1 refers to the first infusion, and subscript 2 refers to the second infusion.

(1). Substitution of $k_0T^2/2$ for $\int_0^\infty Xdt$ (see Eq. 6) in Eq. 8, and recognizing that k_0T equals dose, yields the following equation for V_{ss} for infusion data (6):

$$V_{ss} = \frac{\text{dose}}{AUC}\left(\frac{AUMC}{AUC} - \frac{T}{2}\right) = \text{dose}\,\frac{AUMC}{AUC^2} - \frac{T\ \text{dose}}{2\,AUC} \quad \text{(Eq. 11)}$$

If a case were to arise where input was first-order:

$$V_{ss} = \frac{F\ \text{dose}}{AUC}\left(\frac{AUMC}{AUC} - \frac{1}{k_a}\right) = F\ \text{dose}\,\frac{AUMC}{AUC^2} - \frac{F\ \text{dose}}{k_a\,AUC} \quad \text{(Eq. 12)}$$

If a value of F is not available, V_{ss}/F rather than V_{ss} would be calculated. As is apparent, information other than areas is required to determine V_{ss} where input is other than a bolus.

Administration of drug by multiple modes, for example, a simultaneous bolus plus an infusion, or consecutive infusions, may yield concentration–time data from which it may be desirable to estimate V_{ss}. Equation 9 in conjunction with a more general form of Eq. 8 may be used:

$$\bar{t}_b = \frac{AUMC}{AUC} - \frac{\sum \int_0^\infty X dt}{\sum \text{dose}} \quad \text{(Eq. 13)}$$

Table II—Calculation of V_{ss} for Various Modes of Administration[a]

Mode of Administration	AUC, (μg/ml) hr	$AUMC$, (μg/ml) hr^2	$\frac{AUMC}{AUC}$[b] hr	$\frac{\sum \int_0^\infty X\,dt}{\sum \text{dose}}$ hr	V_{ss}[c] L
IV bolus, 500 mg	1000.0[d]	25002.5[e]	25.0	0	25.0
IV infusion, 250 mg/hr over 2 hr	1000.0	26002.5[f]	26.0	1.0	25.0
First-order administration, 500 mg, $F = 1$, $k_a = 1.4\ \text{hr}^{-1}$	1000.0	25716.8[g]	25.7	0.7	25.0
Bolus plus infusion, 500 mg bolus plus 250 mg/hr over 2 hr	2000.0	51005.0[h]	25.5	0.5	25.0
Two consecutive infusions, 250 mg/hr over 2 hr followed by 41.67 mg/hr over 6 hr	1500.0	40003.7[i]	26.7	1.7	25.0

[a] Calculations based on equation, $C = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t}$, where $A_1 = 60.9545$ μg/ml, $\lambda_1 = 5.0605\ \text{hr}^{-1}$, $A_2 = 39.0459$ μg/ml and $\lambda_2 = 0.03952\ \text{hr}^{-1}$ following a 500-mg bolus dose. [b] See Table I. [c] See Eq. 13. [d] $AUC = \sum_{i=1}^{n} A_i/\lambda_i$. [e] $AUMC = \sum_{i=1}^{n} A_i/\lambda_i^2$. [f] $AUMC = \sum_{i=1}^{n} A_1/\lambda_i^2 + T\,AUC/2$. [g] $AUMC = N/k_a^2 + k_aA_1/\lambda_1^2(k_a - \lambda_1) + k_aA_2/\lambda_2^2(k_a - \lambda_2)$, where $N = k_a$ dose $(k_{21} - k_a)/V_c(\lambda_1 - k_a)(\lambda_2 - k_a)$. [h] Equals c plus d. [i] Use c for two different infusion rates, and add the resulting numbers. Note that only one-half the dose was given on the second infusion.

In Eq. 13, *AUMC* and *AUC* are the total areas under the resulting t C *versus* time and C *versus* time curves, and can be determined in the same manner as outlined for intravenous bolus data (1). The second term on the right hand side of Eq. 13 can be readily solved as the numerator is simply the sum of the $\int_0^\infty Xdt$ values for each mode of administration, and the denominator is the total dose administered by all modes of administration. Examples are illustrated in Table I.

The V_{ss} was determined for the various modes of administration outlined in Table I, utilizing the same data as employed by Benet and Galeazzi (1). All calculations were performed from explicit equations and are presented in Table II. Explicit equations were used to illustrate the validity of the relationships presented here. Estimation of the areas, *AUC* and *AUMC*, from time zero to the first point of the postabsorption and/or postdistribution phase with the linear or logarithmic trapezoidal rule, and from this latter point to time infinity using explicit equations (1) would yield values which vary from the theoretical values. Such variability is primarily due to inherent errors in the methods used to estimate the areas. However, the values obtained would be as reliable as those calculated using traditional methods of data analysis.

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Donald Perrier [x]
Michael Mayersohn
Department of Pharmaceutical Sciences
College of Pharmacy
The University of Arizona
Tucson, AZ 85721

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Albumin Does Not Mediate the Removal of Taurocholate by the Rat Liver

Keyphrases □ Albumin—effect on removal of taurocholate from liver □ Taurocholate—removal from liver not mediated by albumin

To the Editor:

In a recent article by Forker and Luxon (1), the authors discuss what they refer to as a contradiction in liver extraction as a function of albumin concentration and taurocholate free concentration. The authors have failed to relate their experimental observations to a fundamental clearance concept (2):

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$$E = \frac{F_f Cl_I}{Q + F_f Cl_I} \quad \text{(Eq. 1)}$$

Equation 1 can be rearranged to yield:

$$Cl_I = \frac{E\,Q}{F_f\,(1 - E)} \quad \text{(Eq. 2)}$$

where F_f is the free fraction (rather than free concentration) of drug in perfusate, E is the extraction ratio, Q is perfusate flow, and Cl_I is intrinsic clearance by the perfused organ. Using Eq. 2 and the mean data presented by the authors in Tables I and II of their paper (1), (*e.g.*, Q = 4.81 ml/min/g when F_f = 0.57 and E = 0.97 and Q = 4.55 ml/min/g when F_f = 0.11 and E = 0.86), it is apparent that the intrinsic organ clearances are comparable, *i.e.*, Cl_I = 273 and 254 ml/min/g, respectively. The similarity of these intrinsic clearance values indicates that the data generated by Forker and Luxon are consistent with, rather than divergent from, conventional pharmacokinetic theory and that liver uptake can be predicted using free fraction in perfusate and Eq. 2. Therefore, it is apparent that albumin does not mediate the removal of taurocholate by rat liver.

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Wayne A. Colburn
Department of Pharmacokinetics and Biopharmaceutics,
Hoffmann-La Roche, Inc.
Nutley, NJ 07110

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Effect of Plasma Protein Binding on Clearance of Drugs Metabolized by Michaelis–Menten Kinetics

Keyphrases □ Plasma protein binding—effect on clearance of drugs metabolized by Michaelis–Menten kinetics □ Michaelis–Menten kinetics—drug metabolism, effect of plasma protein binding

To the Editor:

It is generally known that restrictively bound drugs exhibit increasing clearances as the unbound concentration increases (1–3). However, the applicability of this concept to restrictively bound drugs which are subject to Michaelis–Menten rather than first-order kinetics has not received much attention. Consider a drug cleared exclusively by the liver. If the enzymes mediating its metabolism are saturable and metabolism is further limited by availability of unbound drug, the intrinsic clearance of unbound drug can be described as (4):

$$Cl'_{int} = \frac{V_{max}}{K_m + \alpha \overline{C}_{ss}} \quad \text{(Eq. 1)}$$

where Cl'_{int} is intrinsic clearance of unbound drug, V_{max} is the maximum velocity of the drug metabolizing enzyme, K_m is the concentration of unbound drug in plasma when the rate of metabolism is $V_{max}/2$, $\overline{C}_{ss}$ is the average steady-state plasma concentration of total drug, and α is the unbound fraction[1]. Equation 1 can be rewritten as follows:

$$Cl'_{int} = \frac{V_{max}}{\alpha\left[\frac{K_m}{\alpha} + \overline{C}_{ss}\right]} \quad \text{(Eq. 2)}$$

For a restrictively bound drug eliminated by a single clearing organ, organ clearance and total clearance can be defined in terms of intrinsic organ clearance and the unbound fraction of drug (5) as follows:

$$Cl_{tot} = Cl'_{int}\,\alpha \quad \text{(Eq. 3)}$$

Equation 2 can be rewritten in terms of Cl_{tot} as follows:

$$Cl_{tot} = \frac{V_{max}\alpha}{\alpha\left[\frac{K_m}{\alpha} + \overline{C}_{ss}\right]} \quad \text{(Eq. 4)}$$

which simplifies to:

$$Cl_{tot} = \frac{V_{max}}{\frac{K_m}{\alpha} + \overline{C}_{ss}} \quad \text{(Eq. 5)}$$

Equation 5 shows that Cl_{tot} will increase as α increases, but the magnitude of the increase depends on the values of V_{max}, K_m, and $\overline{C}_{ss}$. Moreover, for a drug such as phenytoin which is restrictively bound and metabolized by a saturable oxidase, the reported values for K_m (6) are really apparent K_m values rather than true K_m values, since they are calculated on the basis of total rather than unbound concentrations. Actual K_m would be given by:

$$K_m = K_{m\ app}\alpha \quad \text{(Eq. 6)}$$

where $K_{m\ app}$ is the apparent K_m. Thus, it should be noted that for a restrictively bound drug:

$$Cl_{tot} = \frac{V_{max}}{K_{m\ app} + \overline{C}_{ss}} \quad \text{(Eq. 7)}$$

The impact of changes in α on Cl_{tot} become more pronounced as K_m increases as shown in Fig. 1. The relationship between Cl'_{tot}/Cl_{tot} *versus* α is unaffected by changes in V_{max}.

Several investigators have shown increased clearances for phenytoin corresponding to increases in the free fraction of the drug. Shand *et al.* (7) perfused phenytoin through isolated rat liver, varying the albumin concentration of the perfusate and consequently the unbound fraction. Their data show a relationship between Cl_{tot} and α similar to that in Fig. 2. Gugler and coworkers (8) reported a doubling of the free fraction and Cl_{tot} in six hypoalbuminemic nephrotic patients compared with six control subjects. However, average steady-state concentrations of total drug were 6.8 and 2.9 mg/liter for controls and nephrotics, respectively, well below the concentrations necessary to saturate the phenytoin oxidase. When $\overline{C}_{ss} \ll K_m/\alpha$, Eq. 7 simplifies to:

$$Cl_{tot} = \alpha\frac{V_{max}}{K_m} \quad \text{(Eq. 8)}$$

If plasma levels are sufficiently high so that metabolism

[1] Cl'_{int} is intrinsic clearance of unbound drug as defined by Wilkinson and Shand [G. Wilkinson and D. Shand, *Clin. Pharmacol. Ther.* 18, 377 (1975)], and is equivalent to Cl_{int} of Rowland *et al.* (4).

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