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

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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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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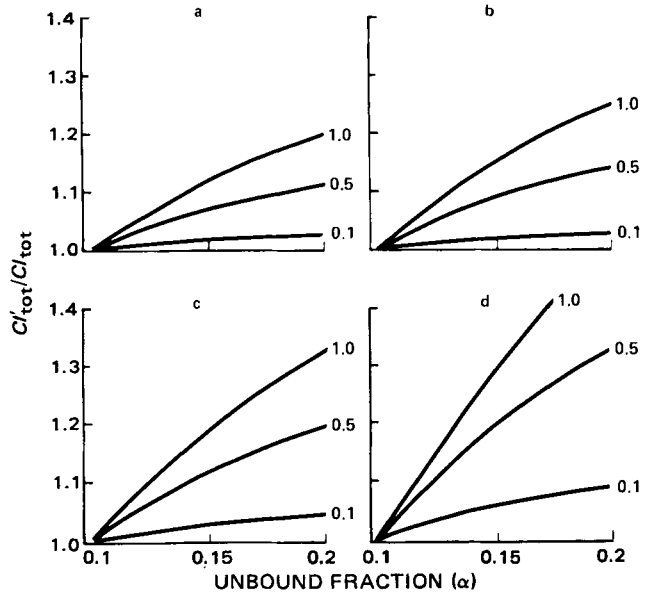

Figure 1—*Impact of α on the clearance of a restrictively bound drug metabolized by Michaelis–Menten kinetics.* Cl'_{tot} *is clearance when* $\alpha > 0.1$. Cl_{tot} *is clearance at* $\alpha = 0.1$. *Actual* K_m *values are shown for each curve.* $\bar{C}_{ss}$ *is 20, 15, 10, and 5 mg/liters for graphs a, b, c, and d, respectively.*

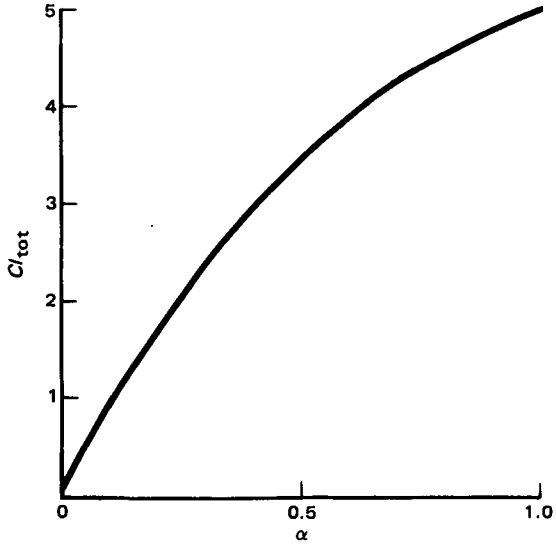

Figure 2—*Relationship between steady-state clearance and magnitude of unbound fraction for a restrictively bound drug metabolized by Michaelis–Menten kinetics.* $\bar{C}_{ss} = 1$ *mg/liter,* $V_{max} = 10$ *mg/hr, and* $K_m = 1$ mg/liter.

is no longer operating by apparent first-order kinetics, the changes in Cl_{tot} will no longer be directly proportional to α. As shown in Fig. 1, a doubling of α will only increase Cl_{tot} slightly, and the extent of the increase will also depend on the actual value of K_m and $\bar{C}_{ss}$.

While clearance changes in a complex manner with altered protein binding, the changes in total and unbound drug concentration are simple. The rate of drug administration required to achieve a targeted average steady-state plasma level is:

$$R_{in} = \frac{V_{max}\bar{C}_{ss}}{\frac{K_m}{\alpha} + \bar{C}_{ss}} \qquad \text{(Eq. 9)}$$

where R_{in} represents the rate of drug administration. If, for example, protein binding were altered by hepatitis, cirrhosis, uremia, heparinization, or drug interaction such that α increased while the rate of administration remained unchanged, the relationship between the total steady-state plasma concentration of drug before and after the change in binding would be:

$$\bar{C}'_{ss} = \frac{\bar{C}_{ss}}{a} \qquad \text{(Eq. 10)}$$

where a is the ratio of altered α to original α, $\bar{C}_{ss}$ is the total plasma concentration before the change, and $\bar{C}'_{ss}$ is the total plasma concentration after the change in binding. From Eq. 10 it is apparent that the average steady-state concentration of free drug is not altered by the change in binding.

The recommendations for adjusting the doses of restrictively bound drugs that are cleared by hepatic metabolism apply to drugs metabolized by either apparent first-order or Michaelis–Menten kinetics when binding is decreased. Though clearance increases, the average steady-state concentration of unbound drug does not. Decreasing the dose and the dosing interval so that the dosing rate remains constant will help to contain peak and trough levels of unbound drug within therapeutic limits.

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