SCIENTIFIC NOTE

Effect of Protein Binding on Steady-State Equations

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Previously published steady-state equations assumed elimination of total drug. The equations have been derived to cover the case where only free (unbound) drug is eliminated. The equation for oral administration is the same in both cases. The equation for intravenous administration has the same form, but the interpretation of K_m is different.

In the article by Wagner *et al.* (1) it was assumed that total drug was eliminated from the liver. Gibaldi and Koup (2) derived their Eqs. (11) and (12) assuming only free drug was eliminated in the liver. If we make the same assumption as Gibaldi and Koup, then our Eq. (30) remains the same, but could also be written as

$$R_0 = \frac{V_m C_{2ss}^{poz}}{K_m + C_{2ss}^{poz}} = \frac{V_m C_{2ss}^{pozf}}{K'_m + C_{2ss}^{pozf}}$$

where $K'_m = f_2 K_m$, $C_{2ss}^{pozf} = f_2 C_{2ss}^{poz}$, f_2 is the free fraction in liver compartment 2, K'_m is the Michaelis-Menten constant in terms of free drug, and the f refers to free (unbound) drug.

Our Eq. (5) would become

$$C_{1ss}^{IV_z} = \frac{R_0}{Q} + \frac{K''_m R_0}{V_m - R_0}$$

where $K''_m = (f_2/f_1) K_m = K'_m/f_1$ and f_1 is the free fraction in blood compartment 1. Thus, if f_1 were measured in blood, then K'_m could be estimated, otherwise K''_m would be estimated. Also, $(K''_m)_{IV}/(K_m)_{po} = f_2/f_1$ and if f_1 is measured directly in blood, then f_2 could be estimated.

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It should be carefully noted that we define the intrinsic clearance of free drug CL_i^f as CL_i/f_u where CL_i is the intrinsic clearance of total drug. Hence our Eq. (49) could be written as

$$CL_H = \frac{QCL_i}{Q+CL_i} = \frac{Qf_uCL_i^f}{Q+f_uCL_i^f}$$

Thus, this obviates the statement of Gibaldi and Koup (2) that writing it as $QCL_i/(Q+CL_i)$ means that drug clearance is independent of drug binding. Similarly, in the symbolism of Gibaldi and Koup (2), we would write $CL_I = f_B CL_I'$. Our definition and equation above agree with the theory and experimental data of Levy and Yacobi (3), who reported that a plot of the clearance of total warfarin versus the fraction unbound gave a linear plot with slope equal to the intrinsic clearance of free drug; this in our symbolism is equivalent to $CL_i = f_u \cdot CL_i^f$.

REFERENCES

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