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Effect of saturable binding on the pharmacokinetics of drugs: a simulation

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The time-courses of both total and unbound drug concentrations with time were simulated under conditions of saturable binding to either plasma proteins or tissues, or both, following a single intravenous dose. The curves were either linear, convex, or concave, depending upon the extent of distribution and the intrinsic ability of an eliminating organ to remove drug from the body. Saturable binding should therefore be considered whenever data showing nonlinear semilogarithmic decline are to be interpreted.

The concentration of unbound drug in plasma is generally assumed to be more closely related to pharmacologic activity than is the total concentration of drug in plasma or blood. Several studies (Anton 1960; Booker & Darcey 1973; Kunin et al 1973; McDevitt et al 1976; Shoeman & Azarnoff 1975; Yacobi & Levy 1975) have indicated the validity of this general assumption, suggesting that the kinetics of the unbound, as well as of the total, drug is of value. Recently, there have been a number of reports describing, both experimentally and theoretically, the influence of protein binding on various pharmacokinetic parameters (Gibaldi et al 1978; Gibaldi & McNamara 1978; Øie & Tozer 1979; Rowland et al 1973; Schoenemann et al 1973; Wilkinson & Shand 1975; Pang & Rowland 1977). However, only a few reports have dealt with the development of pharmacokinetic relationships for the unbound concentration of drug in plasma. When saturable plasma or tissue binding occurs, the unbound and total plasma concentrations are complex functions of time. This situation has been explored in several reports (Martin 1965a, b; Schoenemann et al 1973; Wagner 1976; Coffey et al 1971; Krueger-Thiemer et al 1965; McNamara et al 1979).

In the recently presented model by McNamara et al (1979), clearance was assumed to be either directly proportional to the unbound fraction of drug in plasma or independent of plasma protein binding. These are the two extreme cases of the general relationship among clearance, plasma protein binding and blood flow as suggested by Rowland et al (1973) and Wilkinson & Shand (1975).

Two potential problems arise from the assumptions made in the model by McNamara et al (1979). First, provided the relationship suggested by Rowland et al (1973) and Wilkinson & Shand (1975) is correct, the values chosen for the unbound fraction in plasma and the elimination rate constant give rise to a concentration-dependence in the intrinsic clearance. Second, because more than half of the albumin in the body is outside the vascular system (Jusko & Gretch 1976), saturable protein binding in the tissue compartment also must take place if saturable binding to plasma albumin occurs. This is particularly important when the apparent volume of distribution is small and the binding to albumin outside plasma contributes significantly to the overall binding (Øie & Tozer 1979). In all but two cases of the simulations by McNamara et al (1979) consideration of binding to extravascular, in addition to intravascular, plasma proteins would have altered the outcome of their simulations.

This paper attempts to illustrate the expected temporal relationships for both total and unbound plasma drug concentrations under conditions of saturable binding for drugs whose removal by the organ of elimination is essentially limited either by perfusion or by the intrinsic mechanism of extraction. Recently developed relationships between fundamental pharmacokinetic parameters and binding, both in plasma and in tissues, are used. To limit the number of permutations and combinations possible, a functional, one-compartment model is assumed, and the drug is administered as an intravenous bolus dose, as it best describes disposition characteristics.

METHODS

Model of drug disposition

The model used in the simulations is illustrated in Fig. 1. It implies that there is an instantaneous equilibration of unbound drug throughout the body

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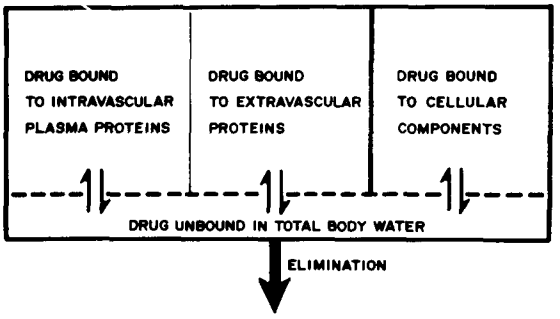

FIG. 1. Model for drug distribution. The unbound drug in total body water is assumed to be at equilibrium with drug bound to intravascular and extravascular plasma proteins, and to intracellular components. Because equilibria are assumed to be maintained, the model is functionally unicompartmental.

and that drug distribution is not limited by blood flow or diffusion into a tissue. Consequently, an alteration in one place of the body is instantaneously reflected throughout the body. Under these conditions, the apparent volume of distribution can be described (Øie & Tozer 1979) by:

$$V = V_P \cdot (1 + R_{E/I}) + \alpha \cdot V_P \cdot \left(\frac{V_E}{V_P} - R_{E/I}\right) + V_R \cdot \frac{\alpha}{\alpha_R} \quad (1)$$

where

V = the apparent volume of distribution
V_P = volume of plasma
$R_{E/I}$ = ratio of extravascular to intravascular amounts of plasma binding proteins
V_E = extracellular-extravascular water space
V_R = intracellular water space
α = unbound fraction of drug in plasma
α_R = the ratio of unbound to total amount of drug distributed intracellularly

Equation 1 provides a means of distinguishing between binding to plasma proteins located in the extracellular-extravascular fluids and binding to other extravascular proteins found elsewhere in the body. This distinction is particularly important when the apparent volume of distribution is small and most of the drug in the body is bound to plasma proteins.

Except for two cases (Cases C and D, Table 1), the plasma binding protein was assumed to be albumin at a concentration of $6 \cdot 10^{-4}$ mol litre^{-1}. In the other two cases, binding to a protein like orosomucoid at a concentration of $1 \cdot 10^{-5}$ mol litre^{-1} with one binding site per molecule was assumed. The value of $R_{E/I}$ was assumed to be 1·2 in all cases. A value of 12 litres was assigned to V_E, extracellular volume minus plasma volume, while a value of 27 litres was assigned to V_R, total body water (Guyton 1976) minus extracellular volume. The volume of plasma, V_P, was given a value of 3 litres. The values of α and α_R were each assumed to follow the general binding isotherm for a protein with one class of binding sites:

$$\alpha_I = \frac{Cu + Kd_I}{Cu + Kd_I + nP_{TI}} \quad (2)$$

where

Cu = the unbound concentration in mol litre^{-1};
Kd_I = the dissociation constant for the drug-macromolecule complex (mol litre^{-1});
nP_{TI} = total concentration of binding sites (mol litre^{-1}).

To illustrate various saturable conditions that may be encountered, the intracellular concentration of binding sites and the value of Kd for plasma and intracellular proteins were varied as described in Table 1 to produce large and small apparent volumes of distribution.

The hepatic blood clearance, Cl_{HB}, has been described by the following relationship (Pang & Rowland 1977):

$$Cl_{HB} = \frac{Q_H \cdot Cl_I \cdot \alpha_B}{Q_H + Cl_I \cdot \alpha_B} \quad (3)$$

where

Q_H = hepatic blood flow;
α_B = ratio of unbound concentration of drug in plasma to total concentration in blood;
Cl_I = intrinsic clearance of drug in the liver.

The value of the intrinsic clearance is characteristic of the metabolic enzyme and the enzyme concentration in the liver. Because enzymatic reactions are saturable, this parameter is expected to show concentration dependence. However, in these simulations this complication was assumed not to occur. In addition, elimination was assumed to occur exclusively in the liver. Conceivably, however, the clearances of drug in other tissues can be described by relationships similar to that of equation 3.

The simultaneous use of equations 1 and 3 is complicated by the volume term being related to the unbound fraction in plasma while the clearance term is a function of the unbound fraction in blood. From equation 3 and the relationships:

$$\alpha \cdot Cp = \alpha_B \cdot C_B \quad (4)$$

$$Cl_H \cdot Cp = Cl_{HB} \cdot C_B \quad (5)$$

where

Cp = drug concentration in plasma

C_B = drug concentration in blood

the hepatic plasma clearance, Cl_H, becomes:

$$Cl_H = \frac{Q_H \cdot Cl_I \cdot \alpha}{Q_H + Cl_I \cdot \alpha \cdot Cp/C_B} \quad (6)$$

However, because the ratio of Cp/C_B is also a function of the fraction unbound, the simultaneous solution of equations 1 and 4 requires knowing this function. In this paper, the amount of drug in the blood cells is assumed to be negligible compared with that in plasma, either because the drug does not enter the blood cells or because there is no binding in the cells. In this situation $Q_H \cdot C_B = Q_P \cdot Cp$, where Q_P, given a value of 900 ml min^{-1}, is the hepatic plasma flow. Thus,

$$Cl_H = \frac{Q_P \cdot Cl_I \cdot \alpha}{Q_P + Cl_I \cdot \alpha} \quad (7)$$

Without the assumption of negligible red blood cell distribution, equations 1 and 6 can be simultaneously solved only when the product, $Cl_I \cdot \alpha \cdot Cp/C_B$ is small compared to Q_H, in which case $Cl_H = \alpha \cdot Cl_I$ at all values of Cp/C_B.

Hepatic plasma clearance, Cl_H, relates the rate of hepatic elimination to the plasma concentration; therefore, after an intravenous bolus dose the rate of change of the amount of drug in the body with time, dAb/dt, is equal to:

$$\frac{dAb}{dt} = -Cl_H \cdot Cp \quad (8)$$

Under saturable protein binding conditions clearance is time- and concentration-dependent. Equation 8 therefore has three time-dependent variables. Its solution requires the relationships among these variables. Using the equation

$$Cp = \frac{Ab}{V} \quad (9)$$

and equations 1, 2, and 7, clearance and plasma concentrations can be expressed in terms of the amount in the body, Ab, and various parameters:

$$Cl_H = f_1(Ab, nP_{TR}, nP_{TP}, Kd_R, Kd_P, Q_P, Cl_I, V_R, V_E, V_P, R_{E/I}) \quad (10)$$

$$Cp = f_2(Ab, nP_{TR}, nP_{TP}, Kd_R, Kd_P, V_P, V_R, V_E, R_{E/I}) \quad (11)$$

where the subscript P denotes plasma and the subscript R denotes cellular location. Equation 8 can now be solved because time and amount of drug in the body are the only variables.

The resulting differential equation, containing a cubic equation, in Cu, was solved by numerical integration using a fourth order Runge-Kutta method (Gear 1971) and the PROPHET computer system (Castleman et al 1974). The cubic equation was solved using a three-point Lagrange interpolation (Muller 1956) within the subroutine ROOT (Risley 1979) available through the PROPHET system. The continuously decreasing real positive root was required for the simulations. The resulting values of the amount in the body with time were used to calculate α, α_R, V, Cp, and Cu at the same time points.

Values for the different parameters were chosen to depict those particularly interesting cases in which saturable plasma protein binding occurs with drugs having either a high or a relatively low volume of distribution and either a high or low intrinsic clearance. The effect of saturable tissue binding was also investigated as well as the situation in which both tissue and plasma binding are saturable and vary in parallel.

RESULTS AND DISCUSSION

The time-course of the amount in the body, the total plasma concentration, and the unbound concentration for the cases of saturable binding given in Table 1 are shown in Figs 2–5. The kinetic consequences of the different cases and the differences between the simulated variables within each case can be explained by how the apparent volumes of distribution of total (V) and unbound drug (V_u), the clearances of total (Cl) and unbound drug (Cl_u), and the elimination rate constant (k) vary with time and by the following interrelationships:

$$Cu = \alpha \cdot Cp \quad (12)$$

$$Ab = V_u \cdot Cu = V \cdot Cp \quad (13)$$

$$Cl_u \cdot Cu = Cl \cdot Cp \quad (14)$$

$$k = \frac{Cl_u}{V_u} = \frac{Cl}{V} \quad (15)$$

Changes in apparent volume of distribution of total drug (Ab/Cp), of unbound drug (Ab/Cu), and in fraction unbound (Cu/Cp) with time are readily observed in the figures by the difference in the logarithms (ratios of numbers) between Ab and Cp curves, Ab and Cu curves, and Cu and Cp curves, respectively, at each time point. The initial and final values of apparent volume of distribution, clearance,

Table 1. Parameters used in the simulations*.

Case	Kd_P (mol litre^{-1})	Kd_R (mol litre^{-1})	nP_{TP} (mol litre^{-1})	nP_{TR} (mol litre^{-1})	Cl_I (litre min^{-1})	Dose (mol)
A	10^{-5}	10^{-2}	$6 . 10^{-4}$	$3 . 10^{-3}$	0·2	$1·5 . 10^{-2}$
B	10^{-5}	10^{-2}	$6 . 10^{-4}$	$3 . 10^{-3}$	1000	$1·5 . 10^{-2}$
C	10^{-7}	$2·5 . 10^{-5}$	10^{-5}	10^{-2}	1	10^{-2}
D	10^{-7}	$2·5 . 10^{-5}$	10^{-5}	10^{-2}	1000	10^{-2}
E	$2 . 10^{-4}$	10^{-7}	$6 . 10^{-4}$	10^{-5}	0·2	$2 . 10^{-3}$
F	$2 . 10^{-4}$	10^{-7}	$6 . 10^{-4}$	10^{-5}	1000	$2 . 10^{-3}$
G	$5 . 10^{-6}$	$5 . 10^{-6}$	$6 . 10^{-4}$	$6 . 10^{-4}$	1	$3 . 10^{-2}$
H	$5 . 10^{-6}$	$5 . 10^{-6}$	$6 . 10^{-4}$	$6 . 10^{-4}$	1000	$3 . 10^{-2}$

* Abbreviations and definitions of parameters are in the text.

and unbound fraction in plasma as well as unbound fraction in tissue are given in Table 2.

Fig. 2 shows the effect of saturable plasma protein binding for drugs with approximately linear binding in the tissues and a small apparent volume of distribution (Cases A and B, Table 1). When a drug has a low intrinsic clearance (left panel, Case A), all three variables decline in a concave manner in a semilogarithmic plot. In this case the value of clearance (Cl_H) is approximately proportional to the unbound fraction (eqn 7, $Q_P \gg Cl_I \cdot \alpha$) as can be seen from the initial and final values in Table 2, while the apparent volume of distribution (V) only changes slightly with a change in the unbound fraction (eqn 1, Table 2). The result is a concave curvature of the log amount versus time. Because the apparent volume of distribution decreases with concentration, the concavity of the log plasma concentration versus time curve is less pronounced in the region shown. The unbound apparent volume of distribution, on the other hand, increases with concentration and the log unbound concentration versus time curve therefore shows a more pronounced concavity in the region shown. These observations are contrary to those of McNamara et al (1979) at the same apparent volume of distribution, 7–21 litres (0·1 to 0·3 litre kg^{-1}). In our simulations concave curves are always seen; convexity in the total plasma concentration versus time curve was observed by these authors (their Fig. 3). The main reason is that these authors did not take into account saturability of binding to plasma proteins located outside plasma.

For a drug with a high intrinsic clearance (right panel, Fig. 2) the effect of saturable plasma protein binding on the three variables is quite different: amount in the body and total plasma concentration show convexity, while unbound concentration declines in a sigmoidal fashion. Changes in amount in the body and in total concentration with time can be explained by a constant clearance, but decreasing unbound and total volumes of distribution. Because the ratio of amount in the body to total plasma concentration is equal to the apparent volume of

Table 2. Initial and final values in the simulations.

Case	Clearance (ml min^{-1}) Init.	Final	App. vol. distr. (litres) Init.	Final	Unbound fract. in plasma Init.	Final	Unbound fract. in tissues Init.	Final
A	52	3	19	8	0·277	0·017	0·773	0·769
B	897	853	19	8	0·277	0·016	0·773	0·769
C	86	11	1000	126	0·095	0·011	0·0026	0·0025
D	892	825	1000	114	0·095	0·010	0·0026	0·0025
E	52	47	19	325	0·276	0·250	0·742	0·021
F	897	897	19	454	0·276	0·250	0·742	0·015
G	219	12	36	34	0·289	0·012	0·289	0·012
H	897	813	36	34	0·289	0·008	0·289	0·008

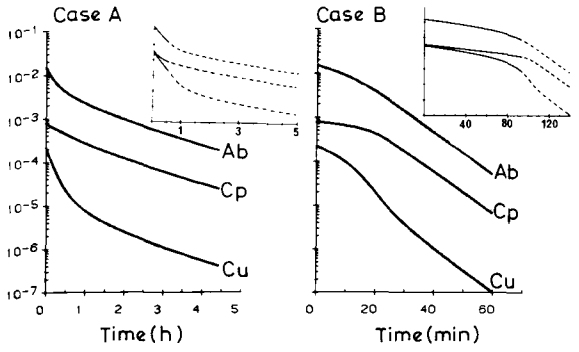

FIG. 2. Effect of saturable plasma protein binding on the time course of amount of drug in the body (Ab, mol), total drug concentration in plasma (Cp, mol litre^{-1}) and unbound drug concentration (Cu, mol litre^{-1}) for a drug with a small apparent volume of distribution. Left panel: drug with low intrinsic clearance (Case A). Right panel: drug with a high intrinsic clearance (Case B). See Table 1 for parameter values. The insets represent the time course for a ten-fold greater dose. (Solid lines, values exceeding those of the main graphs)

distribution and the volume decreases, the total plasma concentration shows a smaller change with time than the amount. The unbound plasma concentration-time curve shows a more complex pattern relative to the amount-time curve, because the unbound volume increases with time.

Insets in Fig. 2 show the time-course of the variables for Cases A and B at doses ten times those listed in Table 1. The stippled lines represent the region covered by the main figure. Note that Cu and Cp are nearly identical and that all three variables decline in parallel under conditions in which α is close to 1·0 and the amount in the body is greater than the dose given in Table 1. Differences in the kinetic consequences of saturable plasma protein binding between low and high intrinsic clearance drugs are particularly notable.

Fig. 3 shows the effect of saturable plasma protein binding for drugs with relatively large apparent volumes of distribution and linear tissue binding (Cases C and D, Table 1). For a drug with a low intrinsic clearance (left panel), the slopes of amount and unbound concentration show essentially no change with time, while the curve of total plasma concentration shows a convex curvature in the region shown. In this case, changes with time in apparent volume of distribution and in clearance are approximately the same, resulting in a constant elimination rate constant and a log-linear decline of the total amount. Because the apparent volume of distribution of unbound drug is essentially constant with time, the decline in unbound concentration parallels that of the total amount. However, because the apparent volume of distribution of total drug decreases, the slope of the total concentration changes with time. In this situation it is important to realize that, although half-life and elimination rate constant do not change with time, the slope of the total plasma concentration-time curve does. The elimination rate constant refers to the amount in the body as illustrated by

$$\frac{dAb}{dt} = -k \cdot Ab \qquad (16)$$

and not to concentrations. A constant half-life or elimination rate constant, therefore, does not necessarily indicate a constant slope of the log concentration-time curve. This only takes place when the apparent volume of distribution is independent of concentration, i.e., when

$$\frac{dAb}{dt} = V \cdot \frac{dC_P}{dt} \qquad (17)$$

For a drug with a high intrinsic clearance and a large volume of distribution (right panel, Fig. 3), the decline of all three variables is convex in nature. At this point the total clearance does remain essentially constant and the apparent volume of distribution decreases with time giving rise to an increasing elimination rate constant. The unbound concentration changes in parallel with that of the total amount because the unbound apparent volume of distribution essentially does not change with time ($V_u \sim V_R$/

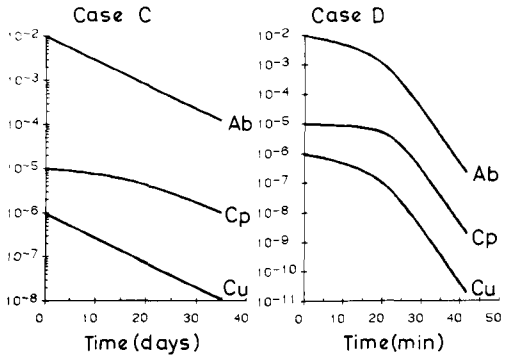

FIG. 3. Effect of saturable plasma protein binding on the time course of amount of drug in the body and total and unbound drug concentrations in plasma, for a drug with a large apparent volume of distribution. Left panel: drug with a low intrinsic clearance (Case C). Right panel: drug with a high intrinsic clearance (Case D). See Table 1 for parameter values and Fig. 2 for units and abbreviations.

α_R). Because the apparent volume of distribution of total drug decreases with decreasing concentration, the log plasma concentration-time curve shows a more pronounced convex curvature in the region shown.

Fig. 4 (Cases E and F) demonstrates the effect of saturable tissue binding for a drug with a low intrinsic clearance (left panel) and for one with a high intrinsic clearance (right panel). In these two cases clearance, being independent of intracellular binding, is constant with time, but apparent volume of distribution increases with time. This results in a decreasing elimination rate constant and a concave curvature in the total amount in the body. The decline of the total concentration is greater than that of the total amount due to an increase in the apparent volume of distribution with time. The unbound concentration is parallel to the total concentration because the unbound fraction in plasma is approximately constant and the unbound and total apparent volumes of distribution change in parallel.

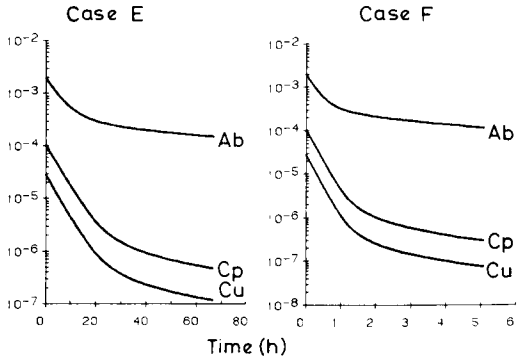

FIG. 4. Effect of saturable tissue binding on the time course of amount of drug in the body and total and unbound concentrations in plasma. Left panel: drug with low intrinsic clearance (Case E). Right panel: drug with a high intrinsic clearance (Case F). See Table 1 for parameter values and Fig. 2 for units and abbreviations.

Fig. 5 (Cases G and H) shows the effect of concurrently saturable plasma protein and tissue binding. In these cases, α and α_R change in proportion. This results in an almost constant apparent volume of distribution with time. For a drug with low intrinsic clearance (left panel) clearance decreases with time. The total amount in the body therefore shows concave curvature as does the total concentration. The unbound concentration shows a more pronounced concavity because the unbound volume of distribution decreases with time. For a drug with high intrinsic clearance (right panel), clearance does not change with concentration, resulting in a log-linear decline in the amount in the body. With an insignificant change in the apparent volume of distribution, the plasma concentration also shows a log-linear decrease with time. The unbound apparent volume of distribution, on the other hand, increases with time to a limiting value, resulting in a sigmoidal curvature in the unbound concentration.

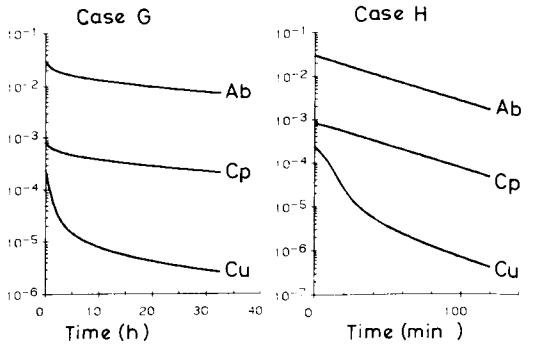

FIG. 5. Effect of concurrent saturable plasma protein and tissue binding on the time course of amount of drug in the body and total and unbound drug concentration in plasma for a drug with an intermediate apparent volume of distribution. Left panel: drug with low intrinsic clearance (Case G). Right panel: drug with a high intrinsic clearance (Case H). See Table 1 for parameter values and Fig. 2 for units and abbreviations.

The possible occurrence of saturable binding must be considered when interpreting plasma concentration-time profiles. Otherwise, inappropriate models may be chosen and predictors based upon them may be invalid. For example, to describe the time-course of a drug showing a concave semilogarithmic decline in the plasma concentration a multicompartmental model is usually chosen. This model is inappropriate for a case of saturable binding as would become apparent on changing the dose administered. Similarly, convex plasma concentration-time profiles have been modelled by invoking capacity-limited metabolism. This model too would be inappropriate if saturable binding is the cause. Consequently, curves potentially showing saturable binding must be carefully interpreted, taking into consideration the volume of distribution and intrinsic clearance of the drug and the probable site at which the saturable binding occurs.

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