CLINICAL PHARMACOLOGY and THERAPEUTICS

volume 36 number 1 July 1984

Commentary

Predictability of verapamil steady-state plasma levels from single-dose data explained

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Wagner et al.[4] used data of Freedman et al.[1] and Shand et al.[2] to construct a plot of $\bar{C}_{ss}/(AUC\ 0-\tau/\tau)$, which is reproduced in this article as Fig. 1. The slope of the line in Fig. 1 is 2.41, much larger than the value of unity expected for a linear system. I was told through the Food and Drug Administration that this figure has been misunderstood by several people as applying universally to all first-pass drugs. This is an unfortunate and erroneous conclusion. A satisfactory explanation of the high correlation indicated by the figure has been derived and is presented below.

Methods

The Appendix shows the derivation of two new equations that give V_m and K_m of the Michaelis-Menten equation as functions of R, Cl_i, and Cl_{ss}. These two equations (Eqs. 9 and 11) apply to both the venous equilibration model and the sinusoidal perfusion model,[3] but the numerical values of Cl_i, Cl_{ss}, V_m, and K_m obtained with both theories will be different (this will be discussed in another article). In Fig. 1, the ratio of ordinate/abscissa is essentially the same as the slope of the least-squares line forced through the origin and is equal to the following when Eqs. 4, 5, and 7 of the Appendix are used:

$$\frac{\bar{C}_{ss}}{AUC\ 0-\infty/\tau} = \frac{AUC\ 0-\tau/\tau}{AUC\ 0-\infty/\tau} = \frac{AUC\ 0-\tau}{AUC\ 0-\infty} = \frac{\frac{D_s}{AUC\ 0-\infty}}{\frac{D_m}{AUC\ 0-\tau}} = \frac{Cl_i}{Cl_{ss}} = \frac{V_m}{V_m-R} \quad \text{(Eq. 1)}$$

If intersubject variation of V_m is small (i.e., narrow distribution), Eq. 1 indicates that all the points of a plot of $\bar{C}_{ss}/(AUC\ 0-\infty/\tau)$ would fall near a straight line, with a slope equal to V_m/V_m-R). Table I lists the estimated values of Cl_i,

Received for publication Jan. 12, 1984; accepted Jan. 27, 1984.

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Abbreviations used

AUC $0-\tau$:	AUC during τ at steady state
AUC $0-\infty$:	AUC from zero to infinity after D_s
Cl_i:	Intrinsic clearance of drug, equal to V_m/K_m and estimated from D_s/AUC $0-\infty$ after a low D_s
Cl_{ss}:	Clearance of drug at steady-state, corresponding to R
C_{ss}:	Steady-state plasma concentration after oral administration at a constant R
$\overline{C}_{ss}$:	Average steady-state plasma concentration after intermittent oral therapy when D_m given every τ hours
D_m:	Maintenance dose of the drug administered orally
D_s:	Single dose of drug
K_m:	Michaelis constant
r:	Correlation coefficient for regression of Y on X
R:	Dosing rate, equal to D_m/τ
τ:	Dosing interval
V_m:	Maximal velocity of metabolism
v:	Instantaneous rate of metabolism at time t, corresponding to C_{ss} or $\overline{C}_{ss}$

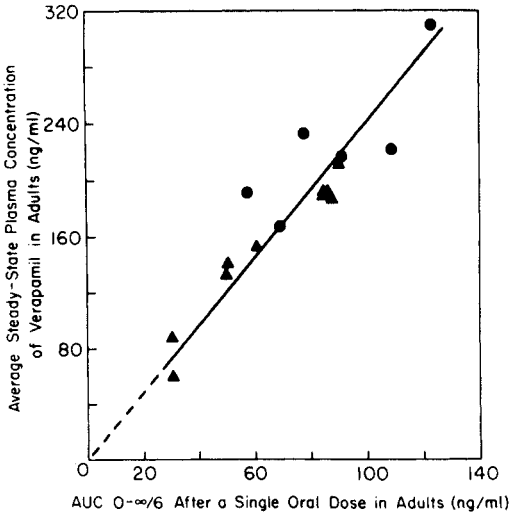

Fig. 1. Plot for predicted $\overline{C}_{ss}$ of verapamil from single-dose oral data in adults. *Triangles* represent data of Freedman et al[1] and *circles* those of Shand et al.[2] Equation of line is: $\hat{Y} = 2.41X$ (n = 15; r = 0.923; $P < 0.001$).

Cl_{ss}, V_m, K_m, Cl_i/Cl_{ss}, $V_m/(V_m-R)$, and $\overline{C}_{ss}$/(AUC $0-\infty$/6). Note that the numeric values of the last three ratios are the same for each subject and the averages are equal to 2.48, essentially the same as the slope of the least-squares line found through the origin in Fig. 1, namely 2.41. Most noteworthy in Table I is the very low intersubject variation in V_m, with a mean of 575 mg/day, a coefficient of variation of 10.7%, and a range of 496 to 711 mg/day. It is this relative constancy of V_m that causes the points in Fig. 1 to be grouped along a straight line with a relatively low degree of scatter.

Discussion

It is feasible with a different first-pass drug than verapamil that V_m would vary more between subjects and hence there would be more scatter in the plot of $\overline{C}_{ss}$/(AUC $0-\infty/\tau$). Hence one should not conclude from the nature of the plot for verapamil (Fig. 1) that other first-pass drugs give similar plots.

Wilkinson et al.[5] defined Cl_i as the volume of water in the liver cleared of the drug per unit time and equal to any oral dose divided by the oral AUC *under first-order conditions*, as well as equal to the ratio V_m/K_m as in Eq. 6 of the Appendix. Many have interpreted this to mean that Cl_i of a given drug in a given person can vary widely depending on the single oral dose administered. I believe this is a misuse of the intrinsic clearance concept, and that each subject given a certain first-pass drug has only one mean Cl_i, which may exhibit some intrasubject variation in estimation from time to time. However, if there is a trend such that estimated clearance decreases with increase in dose or R, then the highest clearance corresponding to the lowest dose or R most closely approaches the actual Cl_i. If several different D_ss have been given or several different Rs have been studied at steady state, the best estimate of Cl_i would be obtained by plotting the estimated clearance against D_s or R, fitting a straight line to the data with the use of the intercept of the line on the ordinate as the estimate of Cl_i. This follows from Eq. 5 of the Appendix, which indicates that a plot of Cl_{ss}/R will be a straight line with an intercept of V_m/K_m and a slope equal to

Table I. *Parameter values for verapamil estimated from single-dose and steady-state plasma concentrations*

Reference for data source	*Subject No.*	Cl_i *(l/min)*	Cl_{ss} *(l/min)*	V_m *(mg/day)*	K_m *(ng/ml)*	Cl_i/Cl_{ss}	$V_m/(V_m - R)$	$C_{ss}/(AUC\ 0 - \infty/6)$*
1†	1	2.640	1.195	585	154	2.21	2.21	2.21
	2	4.474	1.669	510	79.2	2.68	2.68	2.68
	3	3.663	1.468	533	101	2.49	2.50	2.49
	4	7.286	2.589	496	47.3	2.82	2.82	2.81
	5	2.597	1.179	586	157	2.20	2.20	2.21
	6	4.415	1.612	505	79.3	2.74	2.73	2.74
	7	2.545	1.199	605	165	2.12	2.12	2.12
	8	2.465	1.031	547	154	2.39	2.41	2.39
	9	7.366	3.777	657	61.9	1.95	1.95	1.95
2‡	1	3.236	1.343	615	132	2.41	2.41	2.40
	2	2.457	1.027	619	175	2.39	2.39	2.39
	3	2.041	1.006	711	242	2.03	2.03	2.03
	4	1.810	0.723	599	230	2.51	2.51	2.50
	5	2.869	0.955	541	131	3.00	2.99	3.01
	6	3.891	1.170	515	91.9	3.32	3.32	3.33
$\bar{X}$		3.583	1.463	575	133	2.48	2.48	2.48
CV (%)		47.9	52.9	10.7	43.3	15.2	15.1	15.2

*AUC values of Shand et al.[2] were adjusted from the actual dosage interval of 8 hr to those expected for a 6-hr dosage interval (as explained in original article).

†R was 320 mg/day, or 80 mg every 6 hr.

‡R was 360 mg/day, or 120 mg every 8 hr.

$-1/K_m$. As indicated by Eq. 6 of the Appendix, Cl_i is the limit of Cl_{ss} as R approaches 0. First-order kinetics assume that R or D_s are small enough that differences in these values will yield essentially the same value of Cl_i. In the estimation of the verapamil parameter values in Table I, it has been assumed that the Cl_i estimated from a single 80-mg dose of Freedman et al.[1] and the first 120-mg dose of Shand et al.[2] is the actual Cl_i. If these clearances are less than the true Cl_i, then the reported K_m and V_m are higher than the true values, as can be seen from Eqs. 9 and 11 of the Appendix.

I believe that essentially all drugs that exert a significant first-pass effect will exhibit nonlinear Michaelis-Menten kinetics after oral administration at an R in the therapeutic range, as a result of the high drug concentrations entering the liver with this route compared with those after intravenous administration. Support for this statement will be published.

Appendix

When Michaelis-Menten elimination kinetics and the mammillary model with central compartment elimination apply, then v at steady-state is equal to R according to Eq. 2:

$$v = R = \frac{V_m C_{ss}}{K_m + C_{ss}} \tag{2}$$

Rearrangement of Eq. 2 gives Eq. 3:

$$C_{ss} = \frac{K_m R}{V_m - R} = \frac{R}{\left(\frac{V_m - R}{K_m}\right)} \tag{3}$$

and Eq. 4 follows:

$$C_{ss} = \frac{R}{Cl_{ss}} \tag{4}$$

By comparing the denominators of Eqs. 3 and 4, we see that:

$$Cl_{ss} = \frac{V_m - R}{K_m} = \frac{D_m}{AUC\ 0 - \tau} \tag{5}$$

Also, for a low D_s:

$$Cl_i = \frac{V_m}{K_m} = \frac{D_s}{AUC\ 0 - \infty} = \lim_{R \to 0} Cl_{ss} \tag{6}$$

From Eqs. 5 and 6 we obtain Eq. 7:

$$\frac{Cl_{ss}}{Cl_i} = \frac{\frac{V_m - R}{K_m}}{\frac{V_m}{K_m}} = \frac{V_m - R}{V_m} = 1 - \frac{R}{V_m} \quad (7)$$

Rearrangement of Eq. 7 yields Eqs. 8 and 9:

$$\frac{Cl_i}{Cl_{ss}} = \frac{V_m}{V_m - R} \quad (8)$$

$$V_m = \frac{R}{1 - (Cl_{ss}/Cl_i)} \quad (9)$$

From Eqs. 5 and 6 we obtain Eq. 10:

$$Cl_i - Cl_{ss} = \frac{V_m}{K_m} - \frac{(V_m - R)}{K_m} = \frac{R}{K_m} \quad (10)$$

Rearrangement of Eq. 10 gives Eq. 11:

$$K_m = \frac{R}{Cl_i - Cl_{ss}} \quad (11)$$

For intermittent oral or intravenous dosing, R becomes D_m/τ and C_{ss} becomes $\bar{C}_{ss} = AUC\ 0-\tau/\tau$. If unchanged drug is excreted in the urine according to first-order kinetics, R in the above equation must be adjusted for urinary excretion of unchanged drug. If there are "i" metabolites formed in parallel paths, then V_m/K_m is replaced by $\Sigma V_{mi}/K_{mi}$.

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