Prediction of steady-state verapamil plasma concentrations in children and adults

With data on adults from two previous articles it was found that the average steady-state plasma concentration of verapamil in subjects on long-term oral therapy of 80 mg every 6 hr (Y) correlated strongly with the area under the curve from zero to infinity ($AUC^{0-\infty}$/6 (X) where the area refers to that for a single oral dose of 80 mg ($\hat{Y} = 2.41X$, $n = 15$, $r = 0.923$, $P < 0.001$). Steady-state concentrations are predictable from the single-dose data, with an average absolute deviation of 11.1%. We gave seven children (7 to 19 yr old) an initial intravenous bolus dose of 0.1 mg/kg, followed by a 20-min constant rate infusion of 0.007 mg/kg/min. Twenty-four hours after the bolus dose they were put on oral therapy (40 or 80 mg every 6 hr) and 1 mo later the minimum steady-state verapamil plasma concentration (C_{ss}^{min}) was measured. Plasma concentration-time data obtained after the infusion were fitted to biexponential (two sets) or triexponential equations (five sets). The coefficients of the postinfusion polyexponential equations were converted to those for the 0.1-mg/kg bolus dose alone. Mean parameters estimated were: plasma clearance 0.500 l/min, steady-state volume of distribution 279 l, V_β 394 l, half-life 9.17 hr, and mean residence time 10.0 hr. Many correlations were made between the oral C_{ss}^{min} values and functions obtained from the intravenous data. The best correlation was that between C_{ss}^{min} and the predicted steady-state concentration at 3 hr after dosing when bolus doses would be given at 6-hr intervals based on the single-dose intravenous data ($r = 0.985$, $P < 0.001$); this correlation allowed C_{ss}^{min} to be predicted with an average absolute deviation of 10%. Norverapamil was measured in plasma after oral dosing, but was not detectable after intravenous dosing.

John G. Wagner, Ph.D., Albert P. Rocchini, M.D., and John Vasiliades, Ph.D.,
Ann Arbor, Mich.
College of Pharmacy, The Upjohn Center for Clinical Pharmacology, and Departments of Pediatrics and Pathology, University of Michigan

Coronary vasospasm plays a significant role in precipitating myocardial ischemic pain. Verapamil appears to reduce intracellular and, more specifically, sarcolemmal calcium stores in the myocardium and is remarkably effective in preventing coronary spasm[4] and in treating patients with hypertrophic cardiomyopathies.

Verapamil kinetics have been studied in dogs and the changes in arterioventricular conduction time, as estimated from the PR interval of the surface ECG, have been correlated with the logarithm of the plasma verapamil concentration.[10] The kinetics of the drug were also studied in nor-

Supported in part by NIH grant Mo. 1RR00042-21 (Clinical Research Center, University Hospitals).

Received for publication March 1, 1982.

Accepted for publication April 24, 1982.

Reprint requests to: Dr. John G. Wagner, The Upjohn Center for Clinical Pharmacology, University of Michigan, Ann Arbor, MI 48109.

0009-9236/82/080172+10$01.00/0

Abbreviations used

$AUC^{0-\infty}$:	Total area under the concentration-time curve
$AUC^{0-\tau}$:	AUC in dose interval at steady-state
Cl_{po}^{ss}:	Steady-state oral clearance
Cl_{po}^{s}:	Single-dose oral clearance
$\overline{C}_{ss}$:	Steady-state concentration
C_{ss}^{min}:	Minimum steady-state concentration
C_p^{iv}:	Predicted plasma concentration after intravenous dosing
V_{ss}:	Volume of distribution at steady state
GLC:	Gas-liquid chromatography
r^2:	Coefficient of determination
D_{po}/D_{iv}:	Oral/intravenous dose ratio
t½:	Half-life

mal subjects and patients,[1-3, 5-7, 11, 12, 14, 15, 22, 23] but kinetics in children have not been reported to date.

Koup et al.,[8, 9] Slattery et al.,[17] and Slattery[18] have been remarkably successful in predicting the maintenance dose required to attain a desired drug $\overline{C}_{ss}$ from a single determination of concentration after an initial dose. They have also successfully predicted clearance of chloramphenicol in infants and children from a single serum sample obtained 6 hr after the initial intravenous dose. Indirectly such correlations involve relating $\overline{C}_{ss}$ of a drug to a single concentration measured after an initial dose.

Recently both Freedman et al.[5] and Shand et al.[15] reported that there is a marked reduction in verapamil clearance between the time of the first dose and attainment of steady state. As a result of this, Freedman et al. stated that "kinetic predictions based on single doses will not give reliable estimates for long-term oral dosage."[5] We examined this hypothesis in adults, using the published data of Freedman et al. and Shand et al., and in children, using single-dose intravenous and steady-state oral data we obtained.

Methods

Adults. Freedman et al. reported the plasma verapamil $AUC^{0-\infty}$ after a single oral dose (D_{po}) of 80 mg in nine subjects and the $AUC^{0-\tau}$ after long-term oral doses of 80 mg every 6 hr to the same nine subjects. Shand et al. reported $AUC^{0-\infty}$ after an initial oral dose of 120 mg verapamil in six patients and $AUC^{0-\tau}$ after the seventh dose of 120 mg every 8 hr in the same patients. We estimated both Cl_{po}^{s} and Cl_{po}^{ss} from $D_{po}/(AUC^{0-\infty})$ and $D_{po}/(AUC_{0-\tau})$ from each of the 15 pooled data sets, then correlated Cl_{po}^{ss} with Cl_{po}^{s} using the standard least-squares linear regression method. In addition, the data of Shand et al. were dose adjusted to what would be expected for a unit dose of 80 mg, rather than 120 mg, by multiplying the AUCs by 80/120. The average $\overline{C}_{ss}$ was then estimated as $AUC^{0-6}/6$ with the $AUC^{0-\tau}$ values of Freedman et al., and in a similar manner from the data of Shand et al., but using the adjusted areas rather than AUC^{0-8} and 6 rather than 8 hr. These $\overline{C}_{ss}$ values were correlated with $AUC^{0-\infty}/6$ values by standard least-squares linear regression and least-squares regression where the line is forced through the 0,0 point; for the Shand et al. data the dose-adjusted $AUC^{0-\infty}$s were used in this correlation.

Children. Our subjects were seven children (two girls; five boys; 7 to 19 yr old; mean age 12 yr) with documented hypertrophic cardiomyopathy. Five of the seven patients were found at the time of cardiac catheterization to have a resting systolic left ventricular outflow tract gradient greater than 10 mm Hg. All patients were symptomatic as a result of their disease. The symptoms included: marked resting or postexertional dyspnea (all seven patients), chest pain (six patients), and one or more syncopal episodes (four patients).

Routine biochemical investigations revealed normal renal and hepatic function in all patients. No medications were taken in the preceding 48 hr. All studies were performed in the fasting state and all seven patients were given morphine sulfate and diphenhydramine as premedication.

Verapamil was given intravenously to all patients at the time of cardiac catheterization. Verapamil HCl was injected as an initial intravenous bolus of 0.1 mg/kg over 2 min, followed by a 20-min continuous infusion of 0.007 mg/kg/min. The ECG, systemic arterial, left ventricular, and pulmonary artery pressures were continuously monitored. Blood samples (5 to 7 ml) were drawn before verapamil, just as the infusion ceased (0 time), and at 0.1, 0.25,

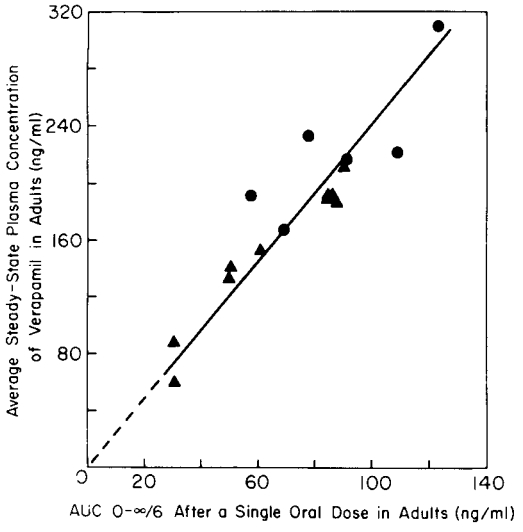

Fig. 1. Plot for prediction of average plasma C_{ss} of verapamil from single-dose oral data in adults. *Diamonds* represent data of Freedman et al.[5] and *circles* of Shand et al.[15] Equation of line is $\hat{Y} = 2.41X$ ($n = 15$, $r = 0.923$, $P < 0.001$).

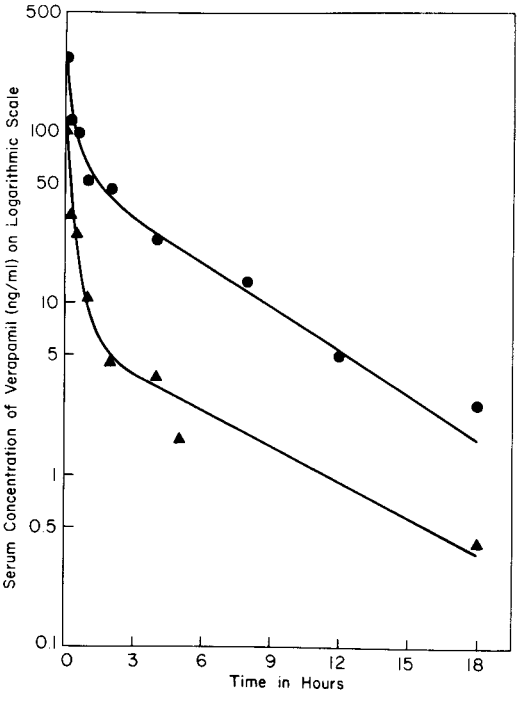

Fig. 2. Semilogarithmic plots of postinfusion data of patients Me *(circles)* and T *(diamonds)*. Lines are computer-fitted concentrations based on equation 1 and the Z_i and λ_i values shown in Table II.

0.5, 1, 2, 4, 8, 12, 16, 18, and 22 hr after the infusion. Blood was transferred to heparinized tubes and centrifuged and the plasma was stored at −20° until analyzed. Oral dosage was initiated (either 40 or 80 mg every 6 hr) 24 hr after the bolus dose and a month later a blood sample was taken at 6 hr after a dose at steady state. The latter samples provided the C_{ss}^{min}. In one patient (Bo) a single oral dose of 40 mg of verapamil was given 24 hr after the intravenous bolus dose and initiation of the 20-min infusion. For this patient blood was also collected just before oral dosing (0 time) and at 0.25, 0.5, 0.75, 1, 2, 3, and 4 hr after dosing. Verapamil and norverapamil were measured in plasma by a sensitive and specific GLC procedure with a nitrogen-sensitive detector.[19]

Postinfusion verapamil plasma concentrations were computer fitted by the method of least-squares as follows:

$$C_p^{iv} = \sum_{i=1}^{n} Z_i\, e^{-\lambda_i t} \qquad (1)$$

where $n = 2$ or 3, Z_i is the coefficient of the ith term, λ_i is the exponent of the ith term, and t is time measured from the end of the infusion. Some data sets were fitted with the program NONLIN[13] with the use of central campus large digital computer; the others were fitted with a program written by Dr. J. L. Fox using an Apple II Plus microcomputer. The Z_i coefficients were converted to C_i coefficients by the method of Singhvi[16] to provide:

$$C_p^{iv} = \sum_{i=1}^{n} C_i\, e^{-\lambda_i t} \qquad (2)$$

where the C_is correspond to a bolus dose of 0.1 mg/kg of verapamil only and t is now time after the bolus dose (see footnote to Table II).

A large number of correlations were made to find the optimum parameter to predict the verapamil plasma C_{ss}^{min}s after long-term oral therapy from the intravenous data. In each case the observed C_{ss}^{min}s were used as the X (abscissa) values and an estimated intravenous concentration, corresponding to the oral dose, was calculated from the fitted parameters (coefficients and exponents) obtained from the single-dose intravenous data and used as the Y (ordinate) values. (The estimated intravenous concentrations used are explained in columns 2 and 3 of, and in the footnotes to, Table VI.)

Table I. *Verapamil plasma concentrations measured after infusion of a bolus dose of 0.1 mg/kg and an infusion of 0.007 mg/kg/min over 20 min*

Time postinf (hr)	Plasma concentration (ng/ml)						
	Subject						
	Ma	*Bu*	*V*	*Me*	*T*	*H*	*Bo*
0	253	304	120	268	101	258	56
0.1	—	140	—	—	—	131	45
0.25	89	116	60	114	32	82	—
0.5	51	72	24	99	25	57	—
1	36	—	—	52	10.4	51	26*
2	26	64	19*	47	4.45*	36*	20*
4	13.4*	56*	16*	24*	3.6*	—	12*
8	11.25*	—	14*	13.5*	1.6*	18*	10
12	7.6*	15*	9.5*	5.1*	—	13.4*	—
16	—	—	—	—	—	8.0*	—
18	6.2*	—	—	2.6*	0.4*	—	—
22	—	—	—	—	—	6.0	—

*Points used to estimate the parameters of the equation $C = C_0 e^{-\lambda_z t}$ in Table V. Parameters were estimated by least squares regression with the equation $\ln C = \ln C_0 - \lambda_z t$.

Results

Adults. The correlation of $Y = Cl_{po}^{ss}$ with $X = Cl_{po}^{s}$ gave the regression line $\hat{Y} = 0.421X - 0.044$ ($r = 0.932$, $P < 0.001$); the intercept did not differ significantly from zero. The least-squares line forced through the 0,0 point gave the regression line $\hat{Y} = 0.411X$ ($n = 15$; $r = 0.932$; $P < 0.001$). This correlation (graph not shown) and the random scatter of the six points from the Shand et al. data about the regression line (three of the six points were essentially on the regression line) indicated that adjustments to dosage and dosage interval data to make them compatible with those of Freedman et al. were justifiable.

Correlation of $Y = \overline{C}_{ss}$ with $X = AUC^{0-\infty}/6$ by the method of least squares forced through the 0,0 point gave the regression line $\hat{Y} = 2.41X$ ($n = 15$; $r = 0.923$; $P < 0.001$). The plot is shown as Fig. 1. The mean absolute (sign ignored) deviation of a predicted $\overline{C}_{ss}$ from the observed $\overline{C}_{ss}$ concentration was 18.4 ng/ml or 11.1%. It should be noted that the reciprocal of the slope of the Cl_{po}^{ss} vs Cl_{po}^{s} regression, namely $1/0.411 = 2.43$, is essentially identical with the slope 2.41 of the $\overline{C}_{ss}$ vs $AUC^{0-\infty}/6$ regression, as expected.

Children. Table I lists the verapamil plasma concentrations measured after infusion following the bolus dose of 0.1 mg/kg and constant-rate infusion of 0.14 mg/kg (total intravenous dose, 0.24 mg/kg) given over 20 min. Table II gives the results of computer fitting of the data shown in Table I to equation 1 and also the C_i values corresponding to equation 2 and a single 0.1-mg/kg bolus intravenous dose of verapamil. The sum of squared deviations and r^2s for the fits are also listed in Table II. The last row in Table II lists the percentage contribution of the terminal log-linear phase, i.e., the $C_1e^{-\lambda_1 t}$ term, to the $AUC^{0-\infty}$ corresponding to a single 0.1-ng/kg bolus dose. Results of fitting two of the seven sets of postinfusion data are shown in Fig. 2.

By the use of the intravenous dose of 0.1 mg/kg and the C_i and λ_i values of Table II, kinetic parameters for verapamil in children were estimated by established methods[20, 21] and are listed in Table III. In addition, the last row of Table III lists the percentage of error in the clearance of verapamil if only the monoexponential equation $C_p = C_1e^{-\lambda_1 t}$ is used rather than the polyexponential equation 2 (see footnote to Table III for the appropriate equations to make such estimates).

Table IV lists the oral doses given to the children, the D_{po}/D_{iv}s used in subsequent correlations, and the measured plasma C_{ss}^{min}s of ver-

Table II. *Parameters from nonlinear least-squares fitting of postinfusion verapamil plasma concentrations after a bolus dose of 0.1 mg/kg and the infusion of 0.14 mg/kg given at a rate of 0.42 mg/kg/hr (0.007 mg/kg/min) over 0.333 hr (20 min)*

Parameter	Subject		
	*Ma**	*Bu*†	*V**
λ_1 (hr^{-1})	0.0391 (0.0316)	0.0737 ‡	0.0405 (0.0518)
λ_2 (hr^{-1})	0.569 (0.168)	3.36	4.07
λ_3 (hr^{-1})	6.37 (0.332)	8.62	
Z_1 (ng/ml)	12.78 (5.14)	74.97	17.90 (5.87)
Z_2 (ng/ml)	40.96 (4.92)	100.6	103.0 (7.78)
Z_3 (ng/ml)	199.3 (5.51)	139.4	—
C_1 (ng/ml)	5.325	31.80	7.534
C_2 (ng/ml)	19.49	86.11	100.6
C_3 (ng/ml)	284.7	587.4	—
Σdev^2	6.96	39.2	85.3
r^2‖	0.9999	0.9991	0.9956
$AUC^{0-\infty}$ $\left(\frac{ng}{ml} \times hr\right)$ for 0.1-mg/kg IV bolus dose	215	525	211
% Contribution of terminal log-linear phase to the $AUC^{0-\infty}$¶ for 0.1-mg/kg IV bolus dose	63.3	82.2	88.2

Values in parenthesis are SDs of estimated parameters. The equation fitted to postinfusion plasma concentrations of verapamil was: $C = \sum_{i=1}^{n} Z_i e^{-\lambda_i t}$, where n = 2 or 3 and t = time after cessation of the infusion. The corresponding equation if only the 0.1-mg/kg bolus dose had been administered is: $C = \sum_{i=1}^{n} C_i e^{-\lambda_i t}$, where t = time after injection and $C_i = \frac{Z_i}{\frac{4.2}{\lambda_i} - \left(\frac{4.2}{\lambda_i} - 1\right) e^{-0.333\lambda_i}}$. CV = coefficient of variation; Σdev^2 = sum of squared deviations.

*Data were fitted with the Apple II microcomputer using a program written by Dr. J. L. Fox using equal weights.

†Data were fitted with the program NONLIN written by Dr. C. M. Metzler using the central campus computer with weighting according to the reciprocals of the concentrations.

‡No SDs were obtained since there were too few data points for the number of estimated parameters.

§No SDs were obtained as a result of a problem with the computer program.

‖$r^2 = 1 - \frac{\Sigma dev^2}{s_y^2}$, where $s_y^2 = \Sigma C_i^2 - (\Sigma C_i)^2/N$.

¶% Contribution = $100\frac{C_1}{\lambda_1}/AUC^{0-\infty}$, where $AUC^{0-\infty} = \Sigma C_i/\lambda_i$ corresponding to the 0.1-mg/kg IV bolus dose.

apamil and norverapamil after 1 mo of oral therapy.

With the starred terminal postinfusion plasma concentrations shown in Table I and the equation shown in the footnote to Table I, the parameters C_0, λ_Z, and the t½ ($0.693/\lambda_Z$) were estimated and are shown in Table V. In six of our seven children the t½ estimated as $0.693/\lambda_Z$ was shorter than that estimated as $0.693/\lambda_1$ (Table III). The mean t½ ($0.693/\lambda_Z$) of 6.40 hr and mean t½ ($0.693/\lambda_1$) of 9.17 hr differed by paired t test ($P = 0.05$). This suggests that polyexponential fitting is necessary to estimate the appropriate elimination rate constant and t½.

Subject				*Mean*	*CV (%)*
Me†	*T*†	*H**	*Bo*†		
0.197	0.160	0.0865	0.167	0.109	59.3
§	(0.238)	(0.0281)	(0.0493)		
1.80	2.605	0.949	4.70	2.58	60.5
	(24.8)	(0.563)	(2.19)		
114.3	4.56	11.15	—	—	—
	(56.9)	(0.941)			
57.35	(6.265	36.08	28.70		
	(9.81)	(11.5)	(3.97)		
95.88	51.05	40.99	27.18		
	(1.8×10^3)	(9.74)	(4.73)		
114.7	44.31	180.7	—		
	(1.8×10^3)	(9.16)			
25.04	2.712	15.35	12.44		
59.88	37.67	21.26	29.68		
3121.	49.03	461.1	—		
228.3	70.3	32.5	15.9		
0.9961	0.9991	0.9994	0.9908		
188	42.2	241	180	229	63.6
67.7	40.2	73.6	41.4	65.2	28.6

Table VI summarizes results of the best correlations of the oral C_{ss}^{min} values with functions derived from the single-dose intravenous data in children. The best correlation is that of row A of Table VI and the correlations become progressively poorer as one proceeds to row F. Correlations were made with the functions shown in the third column of Table VI at various times t and only the best correlation (optimum t value) of each type is shown in the table. The functions are as follows: (A) plasma verapamil C_p^{iv} at 3 hr after dosing when bolus intravenous doses are given every 6 hr, (B) plasma verapamil C_p^{iv} at 3 hr after dosing when both bolus doses and infusions are given intravenously, as in our protocol, (C) plasma verapamil C_p^{iv} at 12 hr after a single intravenous bolus dose, (D) plasma verapamil C_p^{iv} at 12 hr after a bolus dose and an infusion, as in our protocol, (E) as in function A except only terminal intravenous data are used (Table V) and t = 4 hr rather than 3 hr, and (F) as in function C except only terminal intravenous data are used and t = 9 hr rather than 12 hr. In all the correlations the predicted intravenous concentrations correspond to the oral doses (as a result of the use of the D_{po}/D_{IV} ratios shown in Table IV). Confirmation of these correlations should not be attempted by experimental means since the oral doses are too high to be given intravenously, but a lower dose could be given and the dose ratio D_{po}/D_{IV} could be used to correct the measured values. It should be noted that as the r^2 and r values decrease, the mean absolute deviations in a predicted C_{ss}^{min} increase considerably (Table VI).

Table VII lists the verapamil and norverapamil plasma concentrations in patient Bo, who was given an oral dose of 40 mg of verapamil 24 hr after the intravenous doses. The equation fitting the verapamil data (footnote to

Table III. *Verapamil kinetics estimated from doses, body weights, and the data in Table II*

Parameter	Subject							Mean	CV (%)
	Ma	*Bu*	*V*	*Me*	*T*	*H*	*Bo*		
Total IV dose (mg	23.0	16.7	11.8	16.3	5.40	11.8	8.16	13.3	44.3
Age (yr)	19	16	12	15	7	8	10	12	37
Body wt. (kg)	95.8	69.5	49.1	67.9	22.5	49.1	34.0	55.4	44.3
Clearance (*l*/min)	0.742	0.221	0.389	0.604	0.888	0.339	0.315	0.500	49.7
V_p (*l*)	31.0	9.88	45.4	2.12	25.2	9.88	80.8	29.2	93.0
V_{ss} (*l*)	735	148	509	128	144	175	111	279	87.6
V_β (*l*)	1139	180	576	184	333	235	113	394	91.9
V_{dext} (*l*)	1800	219	653	271	830	319	115	601	97.6
t½* (hr)	17.7	9.40	17.1	3.51	4.33	8.01	4.15	9.17	65.7
MRT† (hr)	16.5	11.2	21.8	3.53	2.70	8.60	5.87	10.0	70.4
% error in clearance if monoexponential equation used‡	58.0	21.7	13.3	47.7	149	35.9	8.5	47.7	101

V_p = plasma volume; V_{ss} = volume of distribution at steady state; $V\beta$ = volume of distribution area; V_{dext} = volume of distribution extrapolated.

*Elimination $t_{1/2} = 0.693/\lambda_1$.

†MRT = mean residence time = $\Sigma(C_i/\lambda_i^2)/\Sigma(C_i/\lambda_i)$ (see Table II for C_i and λ_i values).

‡% Error = $100\left[\frac{\lambda_1}{C_1}\left(\frac{C_2}{\lambda_2}+\frac{C_3}{\lambda_3}\right)\right]$ for triexponential equation: $C = C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t} + C_3e^{-\lambda_3 t}$ and % error = $100\left[\frac{\lambda_1 C_2}{C_1\lambda_2}\right]$ for biexponential equation: $C = C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t}$.

Table VII) has 0.337 hr^{-1} as the smallest λ_i value, which corresponds to a t½ of 2 hr. Since this t½ is considerably smaller than any other measured (Tables III and VI), we concluded that the 4-hr sampling period was insufficient to define the log-linear phase.

Discussion

Adults. The hypothesis of Freedman et al. that "kinetic predictions based on single doses will not give reliable estimates for long-term oral dosage"[5] appears untenable in light of Fig. 1. From usual linear kinetic theory one would expect the slope of the line in Fig. 1 to be equal to unity. However, the fact that the slope is 2.41 does not detract from the excellent predictability of plasma verapamil $\bar{C}_{ss}$s after long-term oral therapy from the concentrations measured after a single dose of the drug. The slope of 2.41 indicates that the plasma clearance of verapamil decreases 2.4-fold (from 3.6 to 1.5 *l*/min) during the time from administration of the single or first dose to the steady state as clearly pointed out by Freedman et al. and Shand et al. The remarkable thing indicated by the correlation is the relative uniformity of the fractional or percentage reduction in oral clearance (or increase in AUC per 80 mg oral dose) from person to person. The correlation in Fig. 1 involves only oral dosing, hence the first-pass effect is involved in both the single-dose and steady-state results. However, some or all of the factors involved in the first pass, namely bioavailability (or extraction ratio), hepatic clearance, and possibly effective liver blood flow, must change considerably to account for the slope of 2.41. Since the individual subject verapamil plasma concentrations after the single or first doses and those obtained at steady state were not available in the articles of Freedman et al. and Shand et al., single-point correlations, as described by others,[8, 9, 17, 18] could not be studied, but such studies may be fruitful.

Children. Since there is extensive first-pass metabolism of verapamil the challenge to predict C_{ss}^{min} for long-term oral therapy from single-dose intravenous data was considerable. When the observed verapamil plasma concen-

Table IV. *Oral doses and plasma C_{ss}^{min}s of verapamil and norverapamil after approximately 1 mo of oral dosing*

Subject	D_{po} q.i.d.		D_{po}/D_{iv}*	C_{ss}^{min}	
	mg	mg/kg		Verapamil	Norverapamil
Ma	80	0.835	3.48	99	129
Bu	80	1.15	4.79	225	159
V	80	1.63	6.79	136	114
Me	80	1.18	4.92	63	70
T	40	1.78	7.42	25	61
H	40	0.815	3.40	66	—
			Mean for 80 mg =	131	
			Mean for 40 mg =	33	

*The D_{po} used is the mg/kg oral dose shown in column 3. The D_{iv} used was 0.24 mg/kg (0.1 bolus and 0.14 infusion). These dose ratios were used when Z_i was involved, but ratios 2.4 times larger were used with C_i values since they corresponded to D_{iv} values of 0.1 mg/kg.

trations at a given time after infusion (Table I) were correlated with the C_{ss}^{min}s after 1 mo of oral therapy (Table IV), the best correlation was obtained for t = 4 hr and for that correlation (r^2 = 0.751). The latter *is* lower than any r^2 value in Table VI. Hence, for accurate prediction of oral C_{ss}s polyexponential fitting of the intravenous single-dose data was necessary. The concept of "mapping" the parameter space (varying time t in the functions of Table VI) to uncover the optimum time after dosing to use in correlations of $\overline{C}_{ss}$s with these other parameters obtained from single-dose data appears to be novel. This approach with the children's verapamil data has disclosed that, at least in this case, projecting single-dose intravenous data to steady state (A and B, Table VII) considerably improves predictability—i.e., provides higher r^2 values. Also, when estimated intravenous concentrations at different times after a single dose were used in the correlations the predictability appeared to improve as time after dosing increased, but r^2 appeared to approach an asymptotic value as t increased. Such information may be useful in correlations of the type described by other authors.[8, 9, 17, 18]

Our observations, listed in Table VII, concerning length of the blood sampling time are related to other observations we have made concerning data in the literature. The 6-hr sampling period of Dominic et al.[1] was not long enough to reach the true log-linear phase since they reported an average t½ of 1.8 hr, which is considerably shorter than that reported by others.[2, 3, 5, 6, 11, 15, 22] The mean elimination t½ of 9.17 hr that we obtained in children by

Table V. *Parameters of the equation $C = C_0e^{-\lambda_z t}$ estimated from terminal postinfusion data only**

Subject	C_0 (ng/ml)	λ_z (hr^{-1})	$t½$ (hr)
Ma	16.86	0.0579	12.0
Bu	108.2	0.165	4.2
V	21.65	0.0651	10.6
Me	45.33	0.164	4.2
T	6.082	0.153	4.5
H	43.91	0.105	6.6
Bo	33.57	0.257	2.7
Mean	39.4	0.138	6.4
CV (%)	85.2	50.0	

*See footnote to Table I for data used.

polyexponential fitting was longer than the mean t½ of 6.40 hr that we obtained by use of only terminal concentrations; even the latter is longer than the t½ in adults reported by others.[1–3, 5, 6, 11, 15, 22] The mean clearance of 0.500 *l*/min we found in the seven children is also lower than the mean clearances in the range 0.576 to 1.57 *l*/min reported for adults by others.[1, 3, 5, 6, 11, 22] Thus, it appears that both the clearance and elimination rate constant of verapamil may be smaller in children than in adults. This is so even when it is normalized to body weight; the mean clearance was 11.9 (7.32 omitting patient T) ml/min/kg in the seven (or six) children. In general, evaluation of our child data and the adult data of Eichbaum et al.[3] and Kates et al.[6] indicated that normalizing clearances and volumes of distribution of verapamil for body weight does not lower coefficients of variation, but, in fact, usually raises

Table VI. *Prediction of plasma verapamil C_{ss}^{min}s for oral therapy from verapamil plasma concentrations measured after single intravenous doses*

Code	Abscissa, X*	Method of calculation of X	$\hat{Y} = a + bX$		Coefficients†		Mean deviation‡	
			Intercept, a	Slope, b	r^2	r	ng/ml	%
A	$\hat{C}_{ss}(B)$, t = 3, τ = 6	$\frac{D_{po}}{D_{iv}} \sum_{i=1}^{n} \frac{C_i e^{-\lambda_i t}}{1 - e^{-\lambda_i \tau}}$	12.0	0.257	0.971	0.985§	8.43	10.1
B	$\hat{C}_{ss}(B + I)$, t = 3, τ = 6	$\frac{D_{po}}{D_{iv}} \sum_{i=1}^{n} \frac{Z_i e^{-\lambda_i t}}{1 - e^{-\lambda_i \tau}}$	14.6	0.246	0.963	0.981§	9.67	11.7
C	$\hat{C}(B)$, t = 12	$\frac{D_{po}}{D_{iv}} \sum_{i=1}^{n} C_i e^{-\lambda_i t}$	29.4	0.556	0.931	0.965‖	13.0	21.5
D	$\hat{C}(B + I)$, t = 12	$\frac{D_{po}}{D_{iv}} \sum_{i=1}^{n} Z_i e^{-\lambda_i t}$	29.5	1.33	0.930	0.964‖	13.1	21.5
E¶	$\hat{C}_{ss}(B + I)$, t = 4, τ = 6	$\frac{D_{po}}{D_{iv}}\left[\frac{C_0 e^{-\lambda_z t}}{1 - e^{-5.667\lambda_z}}\right]$	−5.5	0.453	0.855	0.924‖	23.7	29.6
F¶	$\hat{C}(B + I)$, t = 9	$\frac{D_{po}}{D_{iv}}\left[C_0 e^{-\lambda_z t}\right]$	−1.7	1.76	0.845	0.919‖	22.1	28.8

*The predicted verapamil concentrations for intravenous therapy correspond to those expected for doses equivalent to the oral doses (Table IV). $\hat{C}_{ss}(B)$ refers to predicted steady-state concentration for bolus doses of 0.1 mg/kg given every τ hr where t is the time after dosing at steady state. $\hat{C}_{ss}(B + I)$ refers to the predicted concentration for a bolus + infusion regimen as used in this study but repeated every τ hr to steady state. $\hat{C}(B)$ and $\hat{C}(B + I)$ refer to predicted concentrations after single bolus doses and bolus + infusion doses.

†r is the correlation coefficient for the linear regression of Y (the observed verapamil C_{ss}^{min} shown in Table IV) and the X shown in columns 2 and 3 above.

‡The mean absolute (sign ignored) deviation of the predicted from the observed verapamil plasma concentration.

§$P < 0.001$.

‖$P < 0.01$.

¶In these correlations only terminal postinfusion data were used (see Tables I and V).

Table VII. *Plasma concentrations of verapamil and norverapamil in subject Bo after 40 mg of oral verapamil 24 hr after a bolus dose of 0.1 mg/kg and an infusion of 0.14 mg/kg over 20 min*

Time after oral dose (hr)	Plasma concentration (ng/ml)	
	Verapamil*	Norverapamil
0	0	0
0.25	74	31
0.5	61	31
0.75	58	44
1	48	31
2	40	37
3	24	17
4	18	18

*Data from 0.25 to 4 hr were fitted by the equation: $C = 70.36e^{-0.337t} + 15.62e^{-2.83t}$ where t = time of oral dosing. The higher value of 0.337 than those shown for λ_1 in Table II suggests that blood was not sampled long enough to observe the terminal log-linear phase.

them. This accounts for the unit of measure in Table III being liters per minute or liters rather than liters per minute per kilogram or liters per kilogram. We also found no significant correlations of ln Y with ln X where Y = clearance, volume of distribution at steady state, volume of distribution area, volume of distribution extrapolated, t½, or mean residence time and X = body weight.

The last rows of Tables II and III indicate that verapamil should not be treated as a single exponential or one-compartment open model drug in therapeutic drug monitoring. At least in the seven children we studied, the error in such an approximation varies greatly from patient to patient.

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