Prediction of Blood Levels after Multiple Doses from Single-Dose Blood Level Data: Data Generated with Two-Compartment Open Model Analyzed According to the One-Compartment Open Model

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Abstract □ Forty sets of single-dose blood levels were simulated by varying the parameters in the equation appropriate to the two-compartment open model with first-order absorption (Model II). Each set was fit by the method of least squares with an iterative nonlinear program and an IBM 360/30 digital computer to the equation appropriate to the one-compartment open model with first-order absorption (Model I). The estimated parameters of Model I were then used to make predictions of maximum, average, and minimum blood levels to be expected after multiple doses of the drug given at uniform intervals of 6 hr. The predicted values were then compared with the actual values derived for Model II. In general, the equation appropriate to Model I fitted the data generated by means of Model II quite well. When V_2 of Model II was eight times V_1, the fitting of the data generated by Model II with Model I was poor, and the prediction of multiple-dose blood levels was poor. When $8 \leq V_1/V_2 \leq 1$ for Model II, the predictions of multiple-dose blood levels made with the Model I analysis were quite accurate. Literature data suggest that the volume ratio has been in the latter range when the two-compartment open model has been elaborated from actual blood level data collected after intravenous administration. Hence, in the practical situation, one may expect the mathematical error introduced by use of Model I in making predictions of multiple-dose blood levels to be relatively small compared with other possible sources of error in such predictions.

Keyphrases □ Blood levels, single dose—multiple-dose prediction □ Model, two-compartment data—one-compartment analysis □ Kinetic equations—one-, two-compartment models □ Equilibrium-state blood levels—prediction

When a fixed dose of a drug is administered in a fixed multiple-dose regimen, the blood levels of drug eventually reach a steady state in which the blood level-time curve during any dosage interval is the same as it is in the preceding and in the following dosage interval. Much of the literature concerning this phenomenon was cited by Wagner *et al.* (1). Since that time, steady-state blood levels have been reported for several drugs including digitoxin (2), diazepam (3), nalidixic acid (4), diphenylhydantoin (5), dimethyl sulfoxide (6), desipramine (7), digoxin (8, 9), and spectinomycin (10).

Prediction of blood levels after multiple doses of a drug may be made by kinetic analysis of blood levels observed after single doses of the drug. The earliest reference appears to be that of Widmark and Tandberg (11). Most of the predictions of multiple-dose blood levels have been made by analyzing the blood levels observed after single doses according to a one-compartment open model. In this type of analysis, the "body" is considered to consist of a single compartment, and the drug is assumed to disappear from this compartment at a first-order rate. The kinetics assumed for the input to the single compartment depend on the method of administration. For example, Wagner and Alway (12) made reasonably accurate predictions of serum concentrations of lincomycin after multiple intravenous infusions when a constant rate or zero-order input rate was assumed. Most commonly, first-order kinetics are assumed for the input, particularly when the drug is administered orally or intramuscularly. Hence, the one-compartment open model with first-order absorption (Model I shown in Scheme I of *Theoretical*) has been used extensively to make such predictions. The equation, appropriate to this model, which gives the concentration of drug as a function of time after a single dose of drug was first published by Teorell (13) and the corresponding multiple-dose equations were given by Dost (14). Krüger-Thiemer (15–22) has made extensive use of these equations to predict multiple-dose blood levels when the drugs are given in fixed dosage regimens. Most of his predictions have been quite accurate. Others (4, 23–30) have used the model with good success both in fitting blood level and urinary excretion data observed after single doses of drugs, and in making predictions of blood levels and urinary excretion after multiple doses of the drugs. Digital computer programs, which aid in the calculations, have been reported (29, 31).

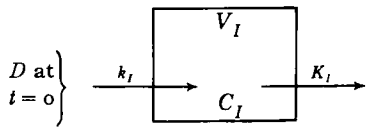
Reasonably accurate predictions of multiple-dose blood levels have been made with this simple Model I despite evidence that (*a*) the absorption of sulfonamides and other drugs is not accurately described by a single first-order rate constant (27, 32–34), and (*b*) the distribution of a drug in the body is better represented by a model with at least two compartments rather than a model having only a single compartment (10, 13, 35–41). This report is directed to an elucidation of the latter.

In practice, when multiple-dose blood levels are predicted from blood levels observed after single doses of drugs, there are several possible sources of error in the predictions. Prediction of average equilibrium-state blood levels involves assumptions that the same fraction of each dose of the multiple-dose regimen is absorbed as was absorbed after the single dose, and that the volume of distribution and rate constant of elimination are the same for each dose of the multiple-dose regimen as for the single dose. Prediction of maximum and minimum blood levels at the equilibrium state, or after a given number of doses, involves the additional assumption that the rate constant for absorption is the same for each dose of the multiple-dose regimen as that following the single dose. Due to inter- and intrasubject variation in all of these parameters, one would expect reasonably accurate prediction of multiple-dose blood levels for the

average of a panel of subjects, but not for the individual subjects. In addition, there is a mathematical error related to the method of analysis of the blood level data observed after single doses. This report is directed to an assessment of the mathematical error associated with predicted multiple-dose blood levels when blood levels which are generated by equations appropriate to a two-compartment open model are analyzed according to the one-compartment open model.

THEORETICAL

Part I—The one-compartment open model with first-order absorption is shown in Model I.



Model I

Here k_I is the estimated first-order rate constant for absorption, K_I is the estimated first-order rate constant for elimination, V_I is the apparent volume of distribution, and C_I is the concentration of drug at time t after administration of the dose, D. For this model, the appropriate multiple-dose equations are as follows.

After n doses of size D, given at uniform time intervals, τ, the concentration, C_I^n, at time t after the nth dose was given by Wiegand *et al.* (28) in their Eq. 13. Their b, a_0, k_a, and k_d become C_I^n, D/V_I, k_I, and K_I, respectively, in the nomenclature of this paper.

The estimated time of the maximum concentration after the nth dose, $\hat{t}^n_{max.}$, is given by:

$$\hat{t}^n_{max.} = \frac{1}{k_I - K_I} \ln \left[\frac{k_I(1 - e^{-K_I\tau})(1 - e^{-nk_I\tau})}{K_I(1 - e^{-k_I\tau})(1 - e^{-nK_I\tau})}\right] \quad \text{(Eq. 1)}$$

The estimated maximum concentration after the nth dose, $\hat{C}^n_{max.}$, is given by:

$$C_{max.} = \left(\frac{D}{V_I}\right)\left(\frac{1 - e^{-nK_I\tau}}{1 - e^{-K_I\tau}}\right)\left[\frac{k_I(1 - e^{-K_I\tau})(1 - e^{-nk_I\tau})}{K_I(1 - e^{-k_I\tau})(1 + e^{-nK_I\tau})}\right]^{(K_I)/(K_I - k_I)} \quad \text{(Eq. 2)}$$

The estimated minimum concentration after the nth dose $\hat{C}^n_{min.}$, is given by:

$$\hat{C}^n_{min.} = \left(\frac{D}{V_I}\right)\left(\frac{k_I}{k_I - K_I}\right)\left[\left(\frac{1 - e^{-nK_I\tau}}{1 - e^{-K_I\tau}}\right)e^{-K_I\tau} - \left(\frac{1 - e^{-nk_I\tau}}{1 - e^{-k_I\tau}}\right)e^{-k_I\tau}\right] \quad \text{(Eq. 3)}$$

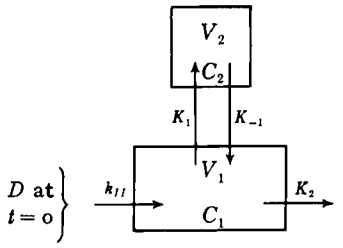
The estimated maximum concentration after an infinite number of doses, $\hat{C}^\infty_{max.}$, is given by:

$$C^\infty_{max.} = \left(\frac{D}{V_I}\right)\left(\frac{1}{1 - e^{-K_I\tau}}\right)\left[\frac{k_I}{K_I}\frac{1 - e^{-K_I\tau}}{1 - e^{-k_I\tau}}\right]^{(K_I)/(K_I - k_I)} \quad \text{(Eq. 4)}$$

The estimated minimum concentration after an infinite number of doses, $C^\infty_{min.}$, was given by Wiegand *et al.* (28) in their Eq. 19. Their $C_{min.}$, a_0, V_d, k_a, and k_d become $C^\infty_{min.}$, D, V_I, k_I, and K_I, respectively, in the nomenclature of this paper.

The estimated average concentration after an infinite number of doses, $C^\infty_{av.}$ was given by Wagner *et al.* (1) in their Eq. 1. In applying the latter equation to this model, F was made equal to unity and V_I and K_I were substituted for V and K, respectively.

Part II—The two-compartment open model with first-order absorption is shown in Model II.



Model II

Here k_{II} is the first-order rate constant for absorption of the Dose, D; K_1 is a first-order distribution rate constant representing the instantaneous fraction of drug in Compartment 1 being transferred to Compartment 2; K_{-1} is a distribution rate constant representing the instantaneous fraction of drug being transferred from Compartment 2 to Compartment 1; K_2 is a first-order rate constant of elimination representing the instantaneous fraction of drug in Compartment 1 which is being lost from Compartment 1; V_1 is the volume and C_1 is the concentration of drug at time t in the inner (No. 1) compartment; and V_2 is the volume and C_2 is the concentration of drug at time t in the outer (No. 2) compartment.

After n doses of size D, given at uniform time intervals, τ, the concentration, C_1^n in the inner compartment at time t after the nth dose, is given by Eq. 5.

$$C_1^n = \left(\frac{k_{II}D}{V_1}\right)\left[\left\{\frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}}\right\}\left\{\frac{K_{-1} - \beta}{(k_{II} - \beta)(\alpha - \beta)}\right\}e^{-\beta t} - \left\{\frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}}\right\}\left\{\frac{K_{-1} - \alpha}{(k_{II} - \alpha)(\alpha - \beta)}\right\}e^{-\alpha t} + \left\{\frac{1 - e^{-nk_{II}\tau}}{1 - e^{-k_{II}\tau}}\right\}\left\{\frac{K_{-1} - k_{II}}{(k_{II} - \alpha)(k_{II} - \beta)}\right\}e^{-k_{II}t}\right] \quad \text{(Eq. 5)}$$

Also,

$$\frac{dC_1^n}{dt} = \left(\frac{k_{II}D}{V_1}\right)\left[\left\{\frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}}\right\}\left\{\frac{\alpha(K_{-1} - \alpha)}{(k_{II} - \alpha)(\alpha - \beta)}\right\}e^{-\alpha t} - \left\{\frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}}\right\}\left\{\frac{\beta(K_{-1} - \beta)}{(k_{II} - \beta)(\alpha - \beta)}\right\}e^{-\beta t} - \left\{\frac{1 - e^{-nk_{II}\tau}}{1 - e^{-k_{II}\tau}}\right\}\left\{\frac{k(K_{-1} - k_{II})}{(k_{II} - \alpha)(k_{II} - \beta)}\right\}\right]e^{-k_{II}t} \quad \text{(Eq. 6)}$$

where,

$$\alpha = \tfrac{1}{2}[(K_1 + K_2 + K_{-1}) + \sqrt{(K_1 + K_2 + K_{-1})^2 - 4K_{-1}K_2}] \quad \text{(Eq. 7)}$$

$$\beta = \tfrac{1}{2}[(K_1 + K_2 + K_{-1}) - \sqrt{(K_1 + K_2 + K_{-1})^2 - 4K_{-1}K_2}] \quad \text{(Eq. 8)}$$

$$K_{-1} = V^*K_1 \quad \text{(Eq. 9)}$$

$$V^* = V_1/V_2 \quad \text{(Eq. 10)}$$

Also, one may define,

$$K^* = K_1/K_2 \quad \text{(Eq. 11)}$$

The time of the maximum concentration in the inner compartment of Model II after the nth dose, $t^n_{max.}$, may be found with an iterative method using Eq. 6. When $(dC_1^n)/(dt) = 0$, then $t = t^n_{max.}$. Similarly, the time of the maximum concentration in the inner compartment of Model II after an infinite number of doses, $t^\infty_{max.}$, may be found by an iterative procedure using a modification of Eq. 6 in which the exponentials containing n are omitted. The maximum concentration in the inner compartment of Model II after the nth dose, $C^n_{max.}$ (for convenience the subscript 1 has been dropped, but the "hat" distinguishes the predicted value obtained for Model I by means of Eq. 2 from this actual value) may be obtained by substituting $t^n_{max.}$ for t in Eq. 5. Similarly, $C^\infty_{max.}$ may be obtained by making a similar substitution into a modification of Eq. 5 in which the exponentials containing n are omitted. The minimum concentration in the inner compartment of Model II at the end of the dosage interval after the nth dose, $C^n_{min.}$, is found by replacing t by τ in Eq. 5. The minimum concentration in the inner compartment after an infinite number of doses is obtained by making a similar replacement in a modification of Eq. 5 in which the exponentials containing n are omitted. The average concentration in the inner compartment of Model II after an infinite number of doses, $C^\infty_{av.}$, is calcu-

Table I—Comparison of Actual Two-Compartment Model Maximum ($C^{\infty}_{max.}$), Average ($C^{\infty}_{av.}$), and Minimum ($C^{\infty}_{min.}$) Concentrations in the Inner (Plasma) Compartment at the Equilibrium State with $C^{\hat{\infty}}_{max.}$, $C^{\hat{\infty}}_{av.}$, and $C^{\hat{\infty}}_{min.}$ Predicted by Means of a One-Compartment Open Model Analysis for the Cases when $k_{II} = 0.5$, $K_2 = 0.15$, $D = 1{,}000{,}000$, and $V_1 = 5{,}000$ in the Two-Compartment Open Model

Set No.	Variables V^*	K^*	Analysis According to One-Compartment Model k_I	K_I	V_I	$\Sigma_{dev.}{}^2$	$(\Sigma_{obs.}{}^2 - \Sigma_{dev.}{}^2)/\Sigma_{obs.}{}^2$	Actual Values for Two-Compartment Model $C^{\infty}_{max.}$	$C^{\infty}_{av.}$	$C^{\infty}_{min.}$	Predicted from One-Compartment Analysis $C^{\hat{\infty}}_{max.}$	$C^{\hat{\infty}}_{av.}$	$C^{\hat{\infty}}_{min.}$	Ratio, Actual:Predicted $C^{\infty}_{max.}/C^{\hat{\infty}}_{max.}$	$C^{\infty}_{av.}/C^{\hat{\infty}}_{av.}$	$C^{\infty}_{min.}/C^{\hat{\infty}}_{min.}$
1	8	0.1	0.529	0.148	5,253	0.584	1.000[a]	246	222	181	238	214	173	1.03	1.04	1.04
2	8	1.0	0.569	0.125	5,915	2.60	1.000	244	222	184	248	225	187	0.98	0.99	0.98
3	8	2.0	0.543	0.127	5,833	3.34	1.000	244	222	184	247	225	187	0.99	0.99	0.98
4	8	10.	0.510	0.132	5,675	0.438	1.000	243	222	185	244	222	185	1.00	1.00	1.00
5	8	100.	0.501	0.133	5,634	0.0111	1.000	243	222	185	244	222	185	1.00	1.00	1.00
6	2	0.1	0.513	0.158	5,108	0.152	1.000	246	222	181	231	207	165	1.06	1.07	1.10
7	2	1.0	0.763	0.109	7,377	7.00	0.999	245	222	184	230	207	170	1.07	1.07	1.08
8	2	2.0	0.806	0.0892	8,239	1.31	1.000	244	222	187	248	227	192	0.98	0.98	0.97
9	2	10.	0.609	0.0893	8,076	19.7	0.9996	238	222	193	249	231	201	0.96	0.96	0.96
10	2	100.	0.510	0.0987	7,565	38.0	1.000	238	222	194	239	223	195	1.00	1.00	0.99
11	1	0.1	0.507	0.161	5,057	0.0378	1.000	246	222	181	229	205	164	1.07	1.08	1.10
12	1	2.0	0.790	0.127	7,467	28.6	0.9994	246	222	184	199	176	138	1.24	1.26	1.33
13	1	2.0	1.005	0.0898	9,494	16.6	0.9996	245	222	188	217	195	162	1.13	1.14	1.16
14	1	10.	0.840	0.0577	11,507	42.0	0.9989	236	222	197	267	251	225	0.88	0.88	0.89
15	1	100.	0.530	0.0721	10,226	2.00	1.000	234	222	200	238	226	204	0.98	0.98	0.98
16	0.125	0.1	0.501	0.164	5,009	0.0108	1.000	246	222	181	227	203	162	1.08	1.09	1.12
17	0.125	1.0	0.605	0.233	5,923	5.26	0.9999	246	222	184	145	121	83	1.70	1.83	2.22
18	0.125	2.0	0.852	0.227	8,054	34.8	0.9987	246	222	187	115	91	57	2.14	2.44	3.28
19	0.125	10.	3.286	0.0839	26,528	74.7	0.9900	239	222	205	89	75	59	2.69	2.96	3.47
20	0.125	100.	0.991	0.0199	45,000	31.3	0.9906	225	222	216	191	186	179	1.18	1.19	1.21
All-over averages														1.21	1.25	1.21
Averages without Sets 17, 18, 19														1.04	1.04	1.05

[a] 1.000 means > 0.9999.

lated by means of Eq. 1 of Wagner *et al.* (1) by letting $F = 1$ and substituting V_1 and K_2 for V and K, respectively. This results in Eq. 12.

$$C_{av.}{}^{\infty} = \frac{\int_{t_1}^{t_2} C_1{}^{\infty}\, dt}{\tau} = \frac{D}{V_1 K_2\, \tau} \qquad \text{(Eq. 12)}$$

where $t_2 - t_1 = \tau$ and $C_1{}^{\infty}$ is the equilibrium-state concentration at time t after dosing. If data are derived from Model II and analyzed according to Model I, then

$$\frac{C^{\infty}_{av.}}{C^{\hat{\infty}}_{av.}} = \frac{\int_{t_1}^{t_2} C_1{}^{\infty}\, dt}{\int_{t_1}^{t_2} C^{\hat{\infty}}\, dt} = \frac{V_1 K_2}{V_I K_I} \qquad \text{(Eq. 13)}$$

Here $\int_{t_1}^{t_2} C_1{}^{\infty} dt$ is the actual area under the C_1, t curve during a dosage interval at the equilibrium state, and $\int_{t_1}^{t_2} C^{\hat{\infty}} dt$ is the predicted area under the curve during a dosage interval at the equilibrium state based on the analysis according to Model I. Also, V_1K_2 is the actual plasma clearance for Model II, while V_IK_I would be the apparent plasma clearance, if data derived from Model II were analyzed according to Model I. Hence, the ratios shown in the second last columns of Tables I and II may be interpreted according to Eq. 13.

EXPERIMENTAL

Forty sets of (C_1, t) data were generated using a digital computer program based on the equation for C_1 after a single dose[1] and Eqs. 7 through 11 for Model II. Analogous to human blood sampling, t was assigned values of 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 14 hr. for each set. D, V_1, and K_2 were held constant with assigned values of 1,000,000, 5000, and 0.15 hr.$^{-1}$, respectively. Twenty sets were generated with $k_{II} = 0.5$ hr.$^{-1}$, and the other 20 sets were generated with $k_{II} = 2.0$ hr.$^{-1}$. Within each group of 20 sets, all possible combinations were generated when V^* was assigned values of 0.125, 1, 2, and 8 and K^* was assigned values of 0.1, 1, 2, 10, and 100. Since there were four values of V^* and five values of K^* this led to a $5 \times 4 = 20$ sets of (C_1, t) values for each value of k_{II}. The 20 sets generated with $k_{II} = 0.5$ hr.$^{-1}$ are assigned numbers 1 through 20 in Table I, and the 20 sets generated with $k_{II} = 2.0$ hr.$^{-1}$ are assigned numbers 21 through 40 in Table II.

Each of these 40 sets of data was analyzed according to Model I. Preliminary estimates of the parameters V_I, k_I, and K_I were obtained by the feathering or back-projection technique using semilogarithmic graph paper, as illustrated by Wagner (44) and Wagner and Metzler (45). It was very difficult in most cases to see the third exponential term, and the data were readily resolvable into only two exponential terms. This phenomenon was mentioned by Riegelman *et al.* (41). Each of the 40 sets of data was fitted by the method of least squares with an iterative digital computer program and an IBM 360/30 digital computer to confrom to the appropriate equation for Model I after a single dose.[2] The graphical estimates of the parameters were used as starting values, and the concentrations were assigned equal weights. The least-squares estimates of the parameters V_I, k_I, and K_I, obtained by this procedure, are those listed in Tables I and II. A typical example of the fits obtained is shown in Fig. 1.

Another digital computer program was then written to calculate the actual values $t^{n}_{max.}$, $C^{n}_{max.}$, and $C^{n}_{min.}$ for $n = 5$, 6, 7, 8, 9, and 100, and $t^{\infty}_{max.}$, $C^{\infty}_{max.}$, $C^{\infty}_{av.}$, and $C^{\infty}_{min.}$ for each of the 40 examples by the methods outlined in *Theoretical*, Part II. The same program was used to calculate $t^{\hat{n}}_{max.}$, $C^{\hat{n}}_{max.}$, and $C^{\hat{n}}_{min.}$ for the same value of n, and $t^{\hat{\infty}}_{max.}$, $C^{\hat{\infty}}_{max.}$, $C^{\hat{\infty}}_{av.}$, and $C^{\hat{\infty}}_{min.}$ for each of the 40 examples by the methods outlined in *Theoretical*, Part I; the least-squares estimates of k_I, V_I, and K_I were substituted into the equations to calculate these predicted values of the multiple-dose blood levels. In all cases, τ was assigned a value of 6 hr. The half-life of elimination, $t_{0.5}$ calculated from K_2 was 4.621 hr; hence, the ratio of $\tau/t_{0.5} = 6/4.621 = 1.30$ in all cases. Hence this ratio is comparable to what would be the real-life situation.

[1] The equation for C_1 was given by Wagner *et al.* (10) as their Eq. 10, p. 283.

[2] See Eq. 30 of Dost (14); for Dost's y, a, k_1, and k_2 the corresponding symbolism in this paper is C_1, D/V_1, k_1, and K_1, respectively.

Table II—Comparison of Actual Two-Compartment Model Maximum ($C^{\infty}_{max.}$), Average ($C^{\infty}_{av.}$), and Minimum ($C^{\infty}_{min.}$) Concentrations in the Inner (Plasma) Compartment at the Equilibrium State with $C^{\hat{\infty}}_{max.}$, $C^{\hat{\infty}}_{av.}$, and $C^{\hat{\infty}}_{min.}$. Predicted by Means of a One-Compartment Open Model Analysis for the Cases when $K_{II} = 2$, $K_2 = 0.015$, $D = 1{,}000{,}000$ and $V_1 = 5{,}000$ in the Two-Compartment Open Model

Set No.	Variables V^*	K^*	Analysis According to One-Compartment Model k_I	K_I	V_I	$\Sigma_{dev.}^2$	$(\Sigma_{obs.}^2 - \Sigma_{dev.}^2)/\Sigma_{obs.}^2$	Actual Values for Two-Compartment Model $C^{\infty}_{max.}$	$C^{\infty}_{av.}$	$C^{\infty}_{min.}$	Predicted from One-Compartment Analysis $C^{\hat{\infty}}_{max.}$	$C^{\hat{\infty}}_{av.}$	$C^{\hat{\infty}}_{min.}$	Ratio, Actual:Predicted $C^{\infty}_{max.}/C^{\hat{\infty}}_{max.}$	$C^{\infty}_{av.}/C^{\hat{\infty}}_{av.}$	$C^{\infty}_{min.}/C^{\hat{\infty}}_{min.}$
21	8	0.1	2.07	0.154	5,104	6.28	1.000[a]	285	222	149	275	212	139	1.04	1.10	1.07
22	8	1.0	2.31	0.134	5,627	4.01	1.000	282	222	154	280	221	153	1.01	1.00	1.01
23	8	2.0	2.24	0.132	5,673	0.286	1.000	280	222	155	280	223	155	1.00	1.00	1.00
24	8	10.	2.06	0.133	5,645	1.15	1.000	278	222	155	278	222	155	1.00	1.00	1.00
25	8	100.	2.005	0.133	5,627	0.0258	1.000	278	222	155	278	223	156	1.00	1.00	0.99
26	2	0.1	2.03	0.161	5,041	1.24	1.000	285	222	149	268	205	132	1.06	1.08	1.13
27	2	1.0	2.78	0.142	6,196	269.	0.9972	286	222	157	247	189	127	1.16	1.17	1.24
28	2	2.0	3.19	0.119	6,918	197.	0.9978	283	222	163	256	202	144	1.11	1.10	1.13
29	2	10.	2.80	0.0968	7,675	7.89	0.9999	266	222	169	270	224	171	0.99	0.99	0.99
30	2	100.	2.06	0.0995	7,527	0.796	1.000	263	222	171	264	222	171	1.00	1.00	1.00
31	1	0.1	2.02	0.163	5,023	0.411	1.000	285	222	149	267	204	131	1.07	1.09	1.14
32	1	1.0	2.71	0.172	6,067	337.	0.8923	287	222	158	219	160	97	1.31	1.39	1.64
33	1	2.0	3.56	0.140	7,273	661.	0.9911	286	222	165	217	164	109	1.32	1.35	1.51
34	1	10.	4.43	0.0775	9,978	18.2	0.9997	265	222	179	255	216	172	1.04	1.03	1.04
35	1	100.	2.21	0.0737	10,100	4.01	0.9999	253	222	182	255	224	184	0.99	0.99	0.99
36	0.125	0.1	2.00	0.164	5,005	0.0176	1.000	285	222	149	266	203	130	1.07	1.09	1.15
37	0.125	1.0	2.14	0.272	5,224	35.9	0.9995	289	222	158	182	117	53	1.59	1.90	2.98
38	0.125	2.0	2.40	0.352	5,652	204.	0.9963	290	222	167	148	84	29	1.96	2.64	5.76
39	0.125	10.	6.72	0.346	11,550	1146.	0.9405	278	222	198	85	42	13	3.27	5.29	15.2
40	0.125	100.	14.6	0.0162	45,000	1.64	0.9997	233	222	211	239	229	218	0.97	0.97	0.97
All-over averages														1.25	1.41	2.15
Averages without Sets 37, 38, 39														1.07	1.08	1.12

[a] 1.000 means > 0.9999.

RESULTS

Due to space limitation, only some of the results of the simulations are presented. Table I lists some of the results for the 20 sets generated when k_{II} was held constant at 0.5 hr.$^{-1}$. Table II lists some of the results for the 20 sets generated when k_{II} was held constant at 2.0 hr.$^{-1}$. From the information supplied in the titles and the columns headed V^* and K^* in these tables, one may calculate the values of the other parameters of Model II. As an illustration, the first entry in Table I gives $V^* = 8$ and $K^* = 0.1$. Since $V_1 = 5{,}000$ and $V^* = 8$, one may calculate the value of V_2 by rearranging Eq. 10; that is, $V_2 = V_1/V^* = 5{,}000/8 = 625$; hence $V_1 + V_2 = 5{,}000 + 625 = 5{,}625$. Since $K_2 = 0.15$ hr.$^{-1}$ and $K^* = 0.1$, one may calculate the value of K_1 by rearranging Eq. 11; that is, $K_1 = K^* K_2 = (0.1)(0.15) = 0.015$ hr.$^{-1}$. By use of Eq. 9, one finds $K_{-1} = V^* K_1 = (8)(0.015) = 0.12$ hr.$^{-1}$. Hence, $K_1 + K_2 + K_{-1} = 0.015 + 0.15 + 0.12 = 0.285$, and, with Eqs. 7 and 8 one finds:

$$\alpha = \tfrac{1}{2}\left[0.285 + \sqrt{(0.285)^2 - (4)(0.12)(0.15)}\right] = 0.19053$$

$$\beta = \tfrac{1}{2}\left[0.285 - \sqrt{(0.285)^2 - (4)(0.12)(0.15)}\right] = 0.09448$$

Analysis according to Model I led to the least-squares estimates of k_I, K_I, and V_I shown in Tables I and II. In about half the cases, k_I agrees reasonably well with the actual rate constant k_{II} (0.5 or 2.0 hr.$^{-1}$), although in all 40 sets $k_I > k_{II}$. In the other half of the cases, k_I was a considerable overestimate of k_{II} and in a few cases, the error was very large. Unlike the situation with the absorption rate constant, K_I was sometimes smaller and sometimes larger than K_2 or β. In all cases, V_I was greater than V_1; usually V_I was greater than V_1, but less than $V_1 + V_2$; however, in some cases, V_I was equal to or greater than $V_1 + V_2$.

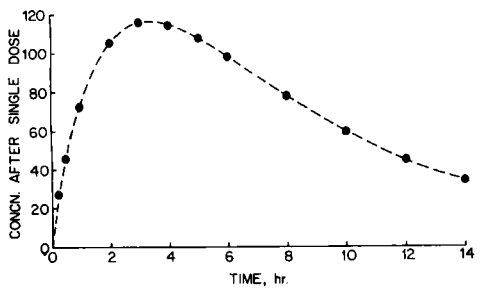


Figure 1—*Dotted line gives one-compartment open model fit to solid dots generated by two-compartment model. Data are for Set 1 of Table I. This is typical of the fits obtained with the majority of the 40 sets of data.*

The actual values, $C^{\infty}_{max.}$, $C^{\infty}_{av.}$, and $C^{\infty}_{min.}$, for the true equilibrium state after an infinite number of doses are given in Tables I and II alongside the predicted values, $C^{\hat{\infty}}_{max.}$, $C^{\hat{\infty}}_{av.}$, and $C^{\hat{\infty}}_{min.}$, based on analysis according to Model I. In the last three columns of Tables I and II are given the ratios $C^{\infty}_{max.}/C^{\hat{\infty}}_{max.}$, $C^{\infty}_{av.}/C^{\hat{\infty}}_{av.}$, and $C^{\infty}_{min.}/C^{\hat{\infty}}_{min.}$. When $8 \leq V^* \leq 1$, the predictions of the maximum, average, and minimum equilibrium state concentrations made from the Model I analysis are quite good. When $V^* = 0.125$ (*i.e.*, $V_2 = 8V_1$) and $100 \leq K^* \leq 1$, analysis according to Model I gave estimates which were much lower than the actual maxima, average, and minima. However, in those cases where Model II has been elaborated from observed blood concentrations of drugs, the volume ratio, V^*, is in the range of about one to three as indicated by the summary in Table III. Based on the data in Table III, it would appear unlikely that V^* would be much less than unity, and most unlikely that it would be as low as 0.125, for a real drug. Hence, in general, *these simulations have shown that prediction of equilibrium-state blood levels by means of Model I can be reasonably accurate when the actual model is Model II.*

Predictions, $C^{\hat{n}}_{max.}$ and $C^{\hat{n}}_{min.}$, made with Model I, where n was 5, 6, 7, 8, 9, 10, and 100 also agreed quite well with the actual values, $C^{n}_{max.}$ and $C^{n}_{min.}$ after the same number of doses. These data were too extensive to include in this report. When $8 \leq V^* \leq 1$, the equilibrium state was essentially reached after the ninth dose (*i.e.*, $n = 9$). This is shown by the ratios given in Table IV. When $V^* = 0.125$, the data were anomalous as indicated by the low values of the ratios in Table IV. When V^* is very small K_{-1} is very small, C_2 is very much greater than C_1 for long periods after each dose, and it requires large number of doses to reach the equilibrium state. This situation would be rare with real drugs as discussed above.

The fits obtained by the method of least squares and Model I to sets of data generated by means of Model II were in general quite good. Results from Set 1 of Table I are plotted in Fig. 1; these results are typical of most of the 40 sets of data. In those cases where the fitting was not good, one could see the third exponential in performing the back-projection technique on semilogarithmic graph paper. Hence, in the practical situation with real blood-level data, one would have warning that Model I may not be appropriate for multiple-dose blood level predictions. The two worst cases of fitting are shown in Figs. 2 and 3. Figure 2 shows the fit for Set 32 of Table II. This set gave the lowest value of 0.8923 for $(\Sigma_{obs.}^2 - \Sigma_{dev.}^2)/\Sigma_{obs.}^2$.

Table III—Average Values of the Parameters of the Two-Compartment Open Model for Panels Given Various Drugs by Rapid Intravenous Injection

Drug	Species	No. Subj.	Average of Individual Parameters of Subjects K_1	K_{-1}	K_2	V_1	$V_1 + V_2$	Ratios Calculated from Averages ($V^* = V_1/V_2$)	($K^* = K_1/K_2$)	Ref.
Creatinine	Dog	10	0.054 min.$^{-1}$	0.059 min.$^{-1}$	0.029 min.$^{-1}$	3,600 ml.	6,860 ml.	1.90	1.8	38
Aldosterone	Man	5	36.5 days^{-1}	76.7 days^{-1}	60.0 days^{-1}	27,000 ml.	40,000 ml.	2.1	0.60	39
1,2-^{3}H-Cortexolone	Man	6	4.11 hr.$^{-1}$	3.69 hr.$^{-1}$	5.52 hr.$^{-1}$	17,600 ml.	36,900 ml.	0.91	0.74	37
Aspirin	Man	3	0.0848 min.$^{-1}$	0.123 min.$^{-1}$	0.111 min.$^{-1}$	6,350 ml.	10,730 ml.	1.88	0.764	42
Salicylic acid	Man	3	0.070 min.$^{-1}$	0.122 min.$^{-1}$	0.0047 min.$^{-1}$	5,630 ml.	9,470 ml.	1.68	15.	42
Griseofulvin	Man	3	0.226 hr.$^{-1}$	0.255 hr.$^{-1}$	0.123 hr.$^{-1}$	60,000 ml.	103,000 ml.	1.39	1.84	42
Spectinomycin	Man	6	0.530 hr.$^{-1}$	1.22 hr.$^{-1}$	0.676 hr.$^{-1}$	7,410 ml.	10,200 ml.	2.66	0.814	10
Lysergic acid diethylamide[a]	Man	5	2.94 hr.$^{-1}$	4.16 hr.$^{-1}$	0.403 hr.$^{-1}$	0.163 l./kg.	0.278 l./kg.	1.42	7.30	43

[a] Parameters are those estimated from average plasma concentrations of the five subjects.

The value of this ratio is analogous to the correlation coefficient of a multiple linear regression. Since there were no errors in the data, a good fit is indicated by a value of this ratio equal to or approaching unity. A low value of the ratio indicates poor fitting. However, in some cases the value of this ratio may be high, but the tail end of the curve may not be fitted well. An example is Set 39 of Table II which is plotted in Fig. 3. Although the value of this ratio was 0.9405 for this set, it is obvious that the fit at the tail end of the curve was very poor. Predictions of multiple-dose concentrations according to Model I for this latter set were the worst of the 40 sets of data as indicated in Table II.

DISCUSSION

The literature suggests that reasonably accurate predictions of maximum, average, and minimum blood levels of drugs after multiple doses may be made by a kinetic analysis of blood levels observed after single doses of the drugs according to Model I. Results reported here suggest that in most cases, simulated blood levels generated with Model II may be fit quite well with the equation appropriate to Model I. Also, in these cases the prediction of multiple-dose blood levels was reasonably accurate despite the fact that the wrong model was employed to make the predictions. The blood level data in this study simulated extremely well the type of blood level curves observed in animals and man after single doses of drugs administered orally and intramuscularly. Hence, the results illustrate that it would be extremely difficult to determine whether the one- or two-compartment open model was the appropriate one in a given case if comparable data were available. A drug must be given intravenously and samples collected shortly after administration to be confident that the two-compartment open model more appropriately describes the data. This was pointed out by Riegelman *et al.* (41, 42).

Hence the validity and usefulness of analysis of single-dose blood level data according to Model I really depends upon what one wishes to do with the numbers one obtains by the analysis. The derived values of the absorption rate constant, the elimination rate constant, and the apparent volume of distribution, obtained by analysis according to Model I, may bear little resemblance to the actual parameters of the model which could be elaborated if more information were available. However, so far as making predictions of multiple-dose blood levels are concerned, these numbers usually are quite satisfactory. On the other hand, use of such absorption rate constants to reflect changes in formulation of a drug, or, use of such elimination rate constants to reflect differences in rate of metabolism of a drug may be misleading.

In those cases in this study where the analysis according to Model I gave poor predictions of multiple-dose blood levels, it was obvious that the simpler model did not provide a good fit to all the blood level data. Such poor fitting of the single-dose blood level data, as illustrated by Figs. 2 and 3, provide a warning signal to the investigator that his predictions may not be satisfactory.

Table IV—Ratios of $C_{max.}$ and $C_{min.}$ after Nine Doses to the Corresponding $C^{\infty}_{max.}$ and $C^{\infty}_{min.}$ after an Infinite Number of Doses for the Two-Compartment Open Model with First-Order Absorption where $V_1 = 5{,}000$, $D = 10^6$, $K_2 = 0.15$ hr.$^{-1}$, $\tau = 6$ hr., and V^* and K^* Varied from Set to Set

Set No.[a]	After 9th Dose and for $k_{II} = 0.5$ hr.$^{-1}$ $C_{max.}/C^{\infty}_{max.}$	$C_{min.}/C^{\infty}_{min.}$	Set No.[a]	After 9th Dose and for $k_{II} = 2$ hr.$^{-1}$ $C_{max.}/C^{\infty}_{max.}$	$C_{min.}/C^{\infty}_{min.}$
4	0.996	1.000	24	1.000	1.000
8	1.000	0.995	28	1.000	1.000
12	0.996	1.000	32	0.996	1.000
16	1.000	1.000	36	0.996	1.000
20	1.000	1.000	40	0.996	1.000
3	0.972	0.961	23	0.975	0.960
7	0.992	0.995	27	0.993	0.994
11	0.992	0.995	31	0.993	0.994
15	0.996	0.995	35	0.996	0.994
19	0.996	0.995	39	0.996	0.994
2	0.951	0.939	22	0.958	0.926
6	0.963	0.962	26	0.972	0.956
10	0.971	0.973	30	0.979	0.970
14	0.975	0.980	34	0.981	0.983
18	0.979	0.985	38	0.980	0.984
1	0.923	0.895	21	0.933	0.872
5	0.699	0.609	25	0.740	0.551
9	0.650	0.567	29	0.707	0.521
13	0.603	0.571	33	0.665	0.565
17	0.582	0.588	37	0.592	0.592

[a] See Tables I and II for values of variables corresponding to each set numbers.

CONCLUSIONS

1. Simulated blood levels of drug derived from the equation appropriate to a two-compartment open model with first-order absorption after a single dose of drug were usually fit well by an equa-

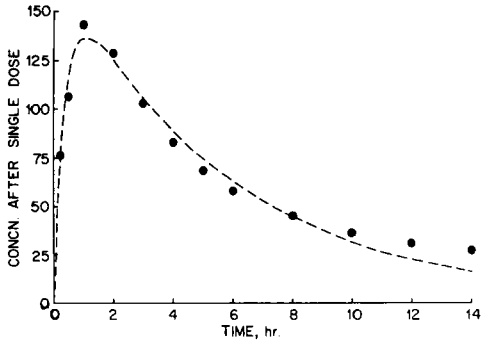


Figure 2—*Dotted line gives one-compartment open model fit to solid dots generated by two-compartment open model. Data are for Set 32 of Table II. This was the worst fit of all 40 sets of data since* $(\Sigma_{obs.}^2 - \Sigma_{dev.}^2)/\Sigma_{obs.}^2$ *had lowest value of 0.8923 for this set.*

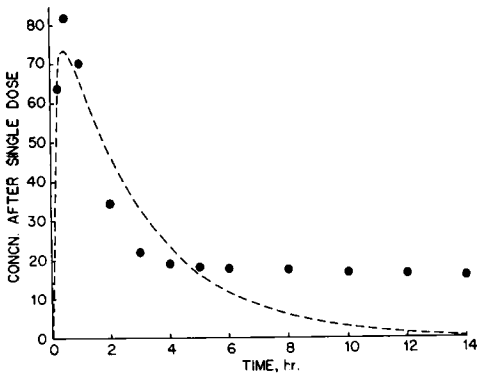


Figure 3—*Dotted line gives one-compartment model fit to solid dots generated by two-compartment model. Data are for Set 39 of Table II. The one-compartment open model parameters estimated in this case led to the poorest predictions of concentrations after multiple dosing. Although* $(\Sigma_{obs.}^2 - \Sigma_{dev.}^2)/\Sigma_{obs.}^2 = 0.9405$ *for this set, it is obvious the fit to the tail end of the curve was quite poor.*

tion appropriate to a one-compartment open model with first-order absorption.

2. Prediction of equilibrium-state blood levels of drug with the one-compartment analysis was usually reasonably accurate.

3. When the volumes of the two-compartment open model were such that V_2 was eight times V_1, the predictions made with the one-compartment analysis were very poor. However, the investigator would be forewarned in such cases since the simpler model provided poor fitting of the single-dose blood level data. Also, the literature indicates that V_1 is usually from one to three times V_2. Hence, the probability that V_2 would be very much larger than V_1 in the two-compartment model would be very low in real life.

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