greatly affected, but the binding of salicylate to Fraction V is greatly diminished. In Fraction V BSA, all of the salicylate binding sites may not be available or readily accessible to the drug. Upon addition of 10 mg.% SETD, however, there may be a subtle conformational change induced by the binding of SETD such that the Fraction V resembles the crystalline BSA in affinity for salicylate. Further studies in progress are directed toward exploration of the nature of the conformational change and its influence on the number of salicylate binding sites and the respective affinity constants.

Binding data were obtained by equilibrium dialysis for 12 hr. at 37°, in pH 7.4, 0.054 *M* phosphate buffer made isotonic with sodium chloride. Both inside and outside solutions were assayed for drug content, utilizing the Bratton-Marshall procedure for SETD (8), and both UV spectrophotometric analysis and ^{14}C were used for determination of salicylate.

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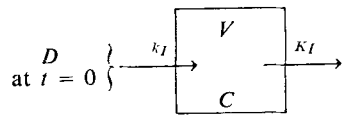
"Absorption Rate Constants" Calculated According to the One-Compartment Open Model with First-Order Absorption: Implications in *In Vivo–In Vitro* Correlations

Keyphrases □ "Absorption rate constants"—one-compartment open model □ *In vivo–in vitro* correlations, "absorption rate constants"—calculation method effect

Sir:

Plasma or serum concentrations of unchanged drug observed following oral administration of single doses of a drug frequently are readily fit by the one-compartment open model with first-order absorption (Model I). Wagner and Metzler (1) cited much of the literature on this fitting; such fitting leads to Eq. 1:



Model I

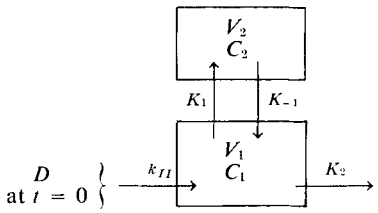
$$C = C^{\circ}\left(\frac{k_I}{k_I - K_I}\right)(e^{-K_I t} - e^{-k_I t}) \qquad \text{(Eq. 1)}$$

Even when simulated data are generated by application of Eqs. 2 and 2*a*,

$$C_1 = \frac{k_{II}D}{V_1}\left[\left\{\frac{K_{-1} - \alpha}{(k_{II} - \alpha)(\beta - \alpha)}\right\}e^{-\alpha t} + \left\{\frac{K_{-1} - \beta}{(k_{II} - \beta)(\alpha - \beta)}\right\}e^{-\beta t} + \left\{\frac{K_{-1} - k_{II}}{(\alpha - k_{II})(\beta - k_{II})}\right\}e^{-k_{II}t}\right] \qquad \text{(Eq. 2)}$$

$$\alpha,\beta = \tfrac{1}{2}\left[(K_1 + K_{-1} + K_2) \pm \sqrt{(K_1 + K_{-1} + K_2)^2 - 4K_{-1}K_2}\right] \qquad \text{(Eq. 2a)}$$

which are appropriate to the two-compartment open model with first-order absorption (Model II), most sets of C_1,t data can be fitted with two exponential terms (Eq. 1) rather than three exponential terms (Eq. 2). With real plasma or serum concentration data observed following oral administration, the same situation exists; however, in some cases, intravenous administration of the same drug tends to dictate the two-compartment open model.



Model II

When correlating "absorption rate constants" derived from plasma concentrations measured in man with *in vitro* rates of drug dissolution from dosage forms, one is most interested in relative values or ratios and not with absolute individual values.

The data in Table I are taken from Wagner and Metzler (1). When apparent "rate constants for absorptions," k_I, were estimated by nonlinear least-squares estimation, by applying Eq. 1 to data generated with Eqs. 2 and 2*a*, the absolute values of k_I deviated from the k_{II} values (either 0.5 or 2.0 hr.$^{-1}$), but the ratios of the k_I values were very close to the ratio of the true k_{II} values (namely, 4.0) when $8 \geq V_1/V_2 = K_{-1}/K_1 \geq 1$. It was previously shown (1) that where Model II was elaborated from actual plasma or serum level data, the ratio of parameters was within the limits shown in Table I.

This observation may help the dilemma of the biopharmaceutical and pharmacokinetic scientist who frequently can fit plasma or serum concentration data, obtained following oral administration, with Eq.

Table I—Parameter Ratios Used to Calculate C_1 Values of Model II and k_I Values and their Ratios Obtained by Fitting the C_1,t Values to Model I[a]

Set No.	$V_1/V_2 = K_{-1}/K_1$	K_1/K_2	k_I when $k_{II} = 0.5$	k_I when $k_{II} = 2.0$	Ratio of k_I's
1	8	0.1	0.529	2.07	3.91
2	8	1.0	0.569	2.31	4.06
3	8	2.0	0.543	2.24	4.13
4	8	10.	0.510	2.06	4.04
5	8	100.	0.501	2.005	4.00
6	2	0.1	0.513	2.03	3.96
7	2	1.0	0.763	2.78	3.64
8	2	2.0	0.806	3.19	3.96
9	2	10.	0.609	2.80	4.60
10	2	100.	0.510	2.06	4.04
11	1	0.1	0.507	2.02	3.98
12	1	1.0	0.790	2.71	3.43
13	1	2.0	1.005	3.56	3.54
14	1	10.	0.840	4.43	5.27
15	1	100.	0.530	2.21	4.17
					Av. 4.05

For Model II, $K_2 = 0.15$, $D = 1{,}000{,}000$, and $V_1 = 5000$ for each set. Note that the ratio of k_{II} values is 4.0. A typographical error in Table II of *Reference 1* gave $K_2 = 0.015$ instead of the actual $K_2 = 0.15$.

1 but not with Eq. 2, even though other data, obtained following intravenous administration, provide strong evidence for Model II or a more complicated model. If he wishes to correlate the apparent "absorption rate constants" derived from application of Model I and Eq. 1, he may be reasonably safe if he utilizes the ratios of the "absorption rate constants" and correlates these with ratios of rates of dissolution or times to dissolve a given percentage of drug derived from an *in vitro* test. I have been quite successful in doing this and will report the details in a future publication.

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BOOKS

REVIEWS

Human Ecology and Public Health. 4th Edition. Edited by EDWIN D. KILBOURNE and WILSON G. SMILLIE. Macmillan, New York, N. Y., 1969. xii + 462 pp. 18 × 26 cm. Price $11.95.

Fairly priced, handsomely printed, sympathetically edited, well illustrated (49 tables; 75 figures), and eminently readable, *Human Ecology and Public Health* is a useful reference for pharmaceutical scientists.

This fourth edition of a work previously entitled *Preventive Medicine and Public Health* relates public health principles to the broader concepts of human ecology. The book is divided into three main divisions—Human Ecology and Human Disease, Public Health Problems and Practice, and the Administration of Health Services; the divisions are subdivided into fifteen chapters. The contributing authors' credentials are excellent; their efforts match their credentials. The references at the conclusion of the chapters are quite comprehensive.

The senior editor describes ecology as an "in" word, and admits to using it with some trepidation. Some examples out of context bear out this concern—on page 85, we learn that "nuclear energy has been harnessed to provide electrical power without polluting the air or depleting natural resources," while on page 90 we are told that the introduction of nuclear reaction power plants has expanded the need for water cooling, "further aggravating the problem" of thermal pollution that alters the life support process of our lakes and streams. We learn of the problems caused by the introduction of synthetic hydrocarbon detergents and are told that the problem was remedied by newly developed biodegradables. No discussion follows about the potential of overloading of surface waters with phosphates, thus upsetting another ecological balance.

Despite these brief lapses from a balanced presentation of bioecology, the book has great merit. Major problem areas—the population explosion, pollution, automobile accidents, and inner-city tensions—are treated with great objectivity. One almost wishes for a touch of the urgent tones of a Commoner (see his *Science and Survival*, for example) when the specific problem of pesticides is considered in Chapter 4, although the purpose of this work does not call on urgency as a teaching device.

Of special note for pharmaceutical scientists are Chapters 2, 3, and 10 which deal, respectively, with Genetic Determinants of Health and Disease; Genetic Interactions of Man and Microbes; and Approaches to the Control of Human Infection. The first two chapters in the division—The Administration of Health Services—are an excellent introduction for the first-time reader and are a