(17) M. Rowland and S. Riegelman, *J. Pharm. Sci.*, **57**, 1313 (1968).
(18) H. Stelmach, J. R. Robinson, and S. P. Eriksen, *ibid.*, **54**, 1453(1965).
(19) J. G. Wagner, E. S. Gerard, and D. G. Kaiser, *Clin. Pharmacol. Ther.*, **7**, 610(1966).
(20) I. S. Sokolnikoff and E. S. Sokolnikoff, "Higher Mathematics for Engineers and Physicists," 2nd. ed., McGraw-Hill, New York, N. Y., 1941, p. 555.
(21) D. S. Riggs, "The Mathematical Approach to Physiological Problems," Williams & Wilkins, Baltimore, Md., 1963, p. 213.
(22) J. G. Wagner and E. Nelson, *J. Pharm. Sci.*, **53**, 1392 (1964).

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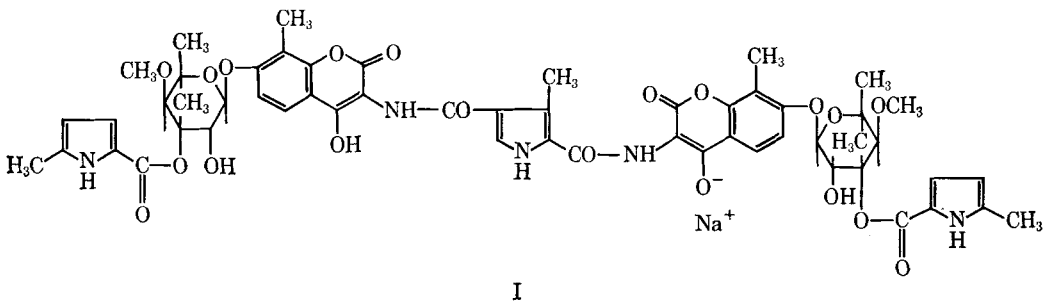
Pharmacokinetic Profile of Coumermycin A_1

STANLEY A. KAPLAN

Abstract □ The pharmacokinetic profile of coumermycin A_1 has been determined in man following intravenous and oral administration. The antibiotic is eliminated slowly from the bloodstream and appears to be highly biotransformed. The plasma level *versus* time curve after intravenous injection is consistent with a two-compartment open system containing a primary compartment with a volume equivalent to the volume of plasma water. The design of a pharmacokinetic model is discussed.

Keyphrases □ Coumermycin A_1—pharmacokinetic profile □ Absorption, elimination—coumermycin A_1 □ Model, two-compartment open—coumermycin A_1 □ Kinetic equations—coumermycin A_1 absorption, elimination

Coumermycin A_1 is an antibiotic isolated from *Streptomyces hazeliensis* var. *hazeliensis* nov. sp. which exhibits antistaphylococcal activity *in vitro* and *in vivo* (1). The compound, a monosodium salt, has a molecular weight of 1132. Coumermycin A_1 is a bishydroxy coumarin with two weakly acidic groups which are widely separated spatially in the molecule and therefore ionize simultaneously with an approximate pKa of 6. The three pyrrole groups are weakly acidic, pKa > 11, and may decrease the solubility of the compound due to hydrogen bonding. The compound is only very slightly soluble in water at 25°. The structure is given as I (2):



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The pharmacokinetic profile of coumermycin A_1 was determined in four human subjects based on the serum level data obtained from the report of a clinical study on file (3, 4).

EXPERIMENTAL

Protocol—Four healthy human adults fasted overnight, received single intravenous and oral doses of coumermycin A_1 at the Special Treatment Unit of Martland Hospital. Subjects A and B each received single 50-mg. doses intravenously and orally, 3 weeks apart. Subjects C and D each received single 100-mg. doses intravenously and orally, 2 weeks apart. The drug was administered in the dosage forms presently used in clinical trials. Blood and urine specimens were collected periodically and the serum separated and frozen for subsequent analysis.

Microbiological Assay—Coumermycin A_1 was analyzed by the cup plate assay employing *Staphylococcus aureus* HLR No. 82. The sensitivity of the method is 0.08 mcg./ml. of biological fluid (4).

RESULTS AND DISCUSSION

The serum level data following both intravenous and oral administration of the drug are presented in Figs. 1–4. Following the intravenous injection of coumermycin A_1, a biexponential serum level curve is obtained with all four subjects. The consideration of the disposition of coumermycin A_1 in terms of a two-compartment open system model is therefore a minimal requirement in order to describe adequately the distribution of the drug into the body. The

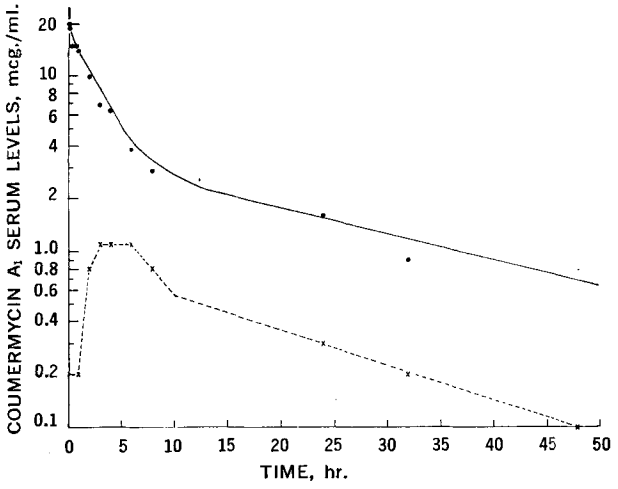


Figure 1—*Coumermycin A_1 serum levels in Subject A following the i.v. and oral administration of a single 50-mg. dose. Key:* ●, *i.v. (data point);* ×- - -, *oral (data point); and* —, *i.v. (calculated curve).*

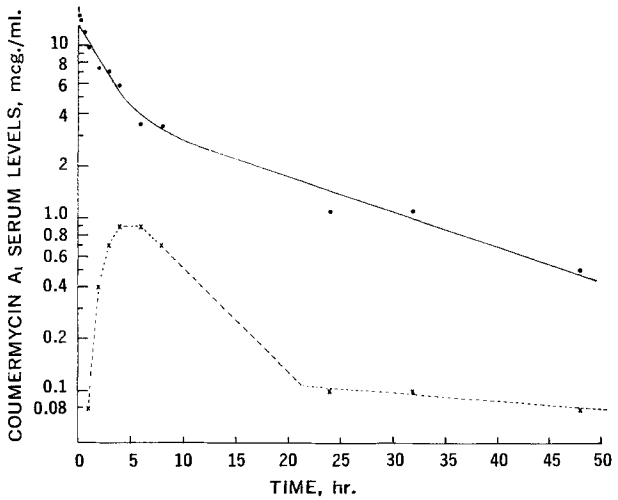


Figure 2—*Coumermycin A_1 serum levels in Subject B following the i.v. and oral administration of a single 50-mg. dose. Key:* ●, *i.v. (data point);* ×- - -, *oral (data point); and* —, *i.v. (calculated curve).*

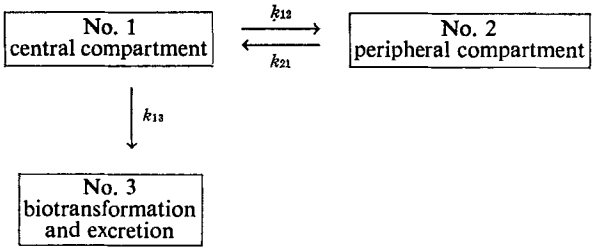
basic equations of the two-compartment open system model have been described by Riegelman *et al.* (5).

Solution of the differential equations resulting from a two-compartment open system model yields the following integrated solution describing the blood level–time curve after a single intravenous injection:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_p is the concentration of the drug in the plasma, A and B are the zero-hour ordinate axis intercepts, and α and β are both hybrid rate constants reflecting all the individual rate processes. The term $-\beta/2.303$ is the slope of the linear portion of the curve and B is its extrapolated zero-hour intercept. Resolving the curve into its two components by the method of residuals yields a second linear segment with a slope of $-\alpha/2.303$ and an extrapolated zero-hour intercept of A.

The disposition data of coumermycin A_1 were evaluated in terms of the two-compartment open system model as described by Riegelman *et al.* (5) Model I, as shown below:



where k_{12} and k_{21} are the first-order rate constants of distribution, and k_{13} is the sum of the simultaneous processes of biotransformation and excretion, all assumed to be first-order processes. The constants, A, B, α, and β, were obtained graphically. They were then used with the appropriate equations to evaluate the rate constants of the two-compartment open model shown above. In addition, the volume of the central compartment (V_p) was determined and found to range in the four subjects studied from 2.6–3.5 l. It is interesting to note that this volume corresponds almost exactly with the volume of the plasma water.

Usually when a single dose of a drug of small molecular size is injected intravenously the blood plasma does not behave as a discernible compartment. Mixing in the plasma is not instantaneous since a few recirculations of blood may be required before mixing is complete. Moreover with small molecules, filtration and diffusion out of the capillary beds is extremely rapid so that by the time the drug is uniformly distributed in the plasma, the drug has already penetrated into a much larger volume. It would be this larger volume, which includes the blood plasma, that constitutes the apparent initial volume of distribution for small drug molecules.

In contrast, coumermycin A_1 is a rather large molecule with a molecular weight of 1132 and is highly bound to plasma albumin (3). In cases where a large molecule is administered, and/or if the molecule is firmly bound, one may be able to identify a separate plasma compartment by analyzing the early part of the curve of serum level *versus* time. In fact, the V_p values of coumermycin A_1 in the four subjects studied bear this out in that the V_p range of 2.6–3.5 l. corresponds directly to the plasma water compartment *per se*. Therefore, the usual concept of a central compartment as defined by Riegelman (5) may be inappropriate for the disposition of coumermycin A_1. In the model for the disposition of coumermycin A_1 the first compartment apparently reflects solely the plasma water, while the second compartment comprises the remaining body distribution space. It is interesting to note that only one other report (6) was found with an example of a defined plasma water compartment, and this too was for a highly bound drug.

In designing a model for the disposition of coumermycin A_1 the following additional factors should be considered. The drug is not eliminated from the central or plasma compartment inasmuch as intact drug is not excreted, and biotransformation can be assumed not to occur in the plasma since the drug is not hydrolyzed or de-

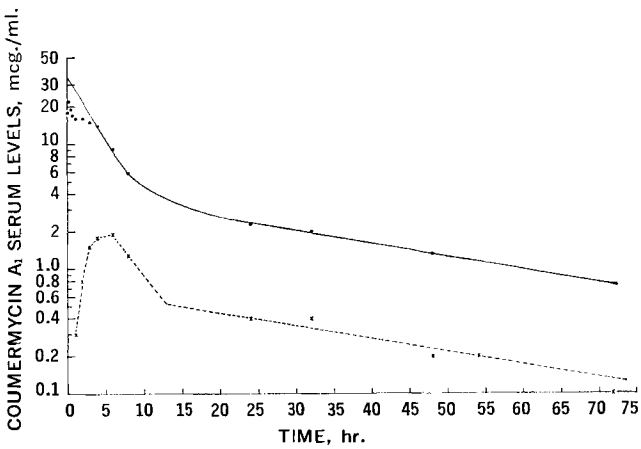
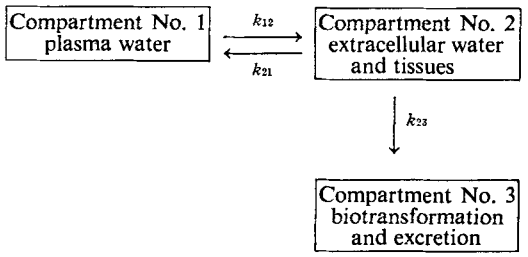


Figure 3—*Coumermycin A_1 serum levels in Subject C following the i.v. and oral administration of a single 100-mg. dose. Key:* ●, *i.v. (data points);* ×- - -, *oral (data points); and* —, *i.v. (calculated curve).*

graded in the plasma. Therefore biotransformation is occurring elsewhere in the body.

The above factors indicate that the appropriate model for the disposition of coumermycin A_1 may then be as follows (Model II):



As with the previously described model the concentration of drug in the plasma, C_p, as a function of time is given by the equation:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

α and β are both hybrid rate constants reflecting all the individual rate processes, while k_{12}, k_{21}, and k_{23} are individual rate constants calculable from this equation, as described in *Appendix I*.

By assigning k_{23} as the elimination rate constant in Model II we make the assumption that Compartment 2 is homogeneous, *i.e.*, the total amount of drug in the compartment is immediately accessible to the elimination mechanism. This assumption would be meaningful if the drug were distributed essentially into the liver. However, Compartment 2 in Model II represents the entire available body space minus the plasma and until such time that tissue level studies are completed the utility of Model II is governed by the accuracy of this assumption.

The rate constants associated with each of the models were calculated and are presented in Table I. In evaluating both models in terms of the disposition of coumermycin A_1, it should be noted that the elimination rate constant, k_{13} as defined in Model I, may be an overestimate of the elimination rate since the model design indicates that only the relatively small fraction of drug in the plasma compartment, Compartment No. 1, is immediately available for elimination. On the other hand the elimination rate constant, k_{23}, in Model II may be an underestimate of the elimination rate for the author is assuming that Compartment 2 is homogeneous with all the drug contained therein immediately available for elimination. The elimination rate constant, therefore could be some value other than k_{13} or k_{23}. It should also be noted that since individual compartments are not detected, the corresponding rate constants into and out of compartments are not specific in that they do not apply to any real compartments.

Although the value of the elimination rate constant is interesting from a purely pharmacokinetic point of view it is not as meaningful physiologically, in terms of the disposition of the drug as is β, the apparent elimination rate of the drug. Therefore, the inability to define the value of the elimination rate constant at this time will not alter the validity of the pharmacokinetic profile of coumermycin A_1 presented herein. In fact, one might wonder in this particular case as to the relevance of the elimination rate constant in defining the physiological disposition of a drug.

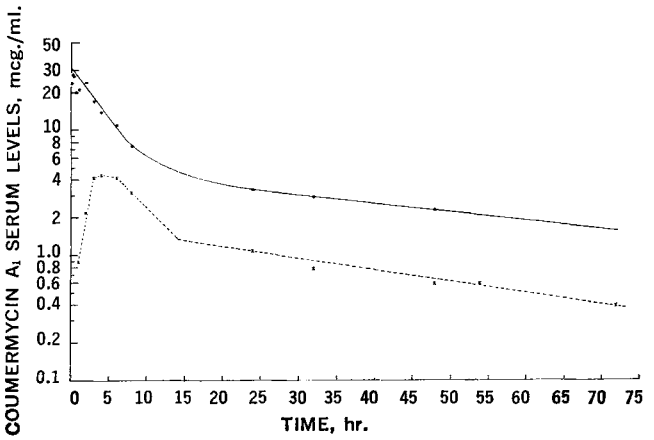


Figure 4—*Coumermycin A_1 serum levels in Subject D following the i.v. and oral administration of a single 100-mg. dose. Key: ●, i.v. (data points); ×- - -, oral (data points); and —, i.v. (calculated curve).*

Physiological Disposition Characteristics of Coumermycin A_1—In describing the physiological disposition of coumermycin A_1 many of the calculated parameters are independent of Models I and II. This model independence results from the fact that certain constants such as *A*, *B*, α, and β are the same for both models. It is these model independent parameters, therefore, which will now be discussed in terms of the pharmacokinetic profile of coumermycin A_1. They are presented in Table II. It should be noted that the simulated intravenous blood level curves in Figs. 1–4 obtained using *A*, *B*, α, and β coincide quite well with the experimentally determined data points.

Elimination Characteristics—The results in Table II indicate that coumermycin A_1 has a fast disposition rate constant, α, which ranged from 25.7–41.2%/hr., corresponding to a half-life of 2.7–1.7 hr. The slow disposition rate constant, β, derived from the slope of the linear segment of the serum level curve reflects the apparent elimination rate of the drug from the body. The slow disposition rate constant, β, ranged from 1.5–4.7%/hr., corresponding to a half-life of 46.3–14.8 hr.

It should be noted that in the four subjects studied there seems to be a trend toward a decreased elimination rate with increase of dose. However, there were too few subjects studied to make any definitive statement at this time. As seen in Table II, as the dose was increased the apparent half-life increased as follows:

Subject	Dose, mg./kg.	Half-Life of Elimination, hr.
B	0.61	14.8
A	0.78	20.6
C	1.02	28.6
D	1.85	46.3

This might be a result of saturation of plasma- or tissue-binding sites and/or saturation of the metabolizing enzymes.

Another parameter, the fraction of drug in the body in the central compartment (*fc*) during the β-phase (7) was found to be very close when calculated with the elimination rate constant from either

Table I—Rate Constants for the Disposition of Coumermycin A_1 as a Function of Model

Subject	A		B		C		D	
α, hr.$^{-1}$	0.405		0.412		0.306		0.257	
β hr.$^{-1}$	0.034		0.047		0.024		0.015	
A, mcg./ml.	15.85		9.82		31.85		28.03	
B, mcg./ml.	3.48		4.49		4.20		4.71	
	Model I	Model II	Model I	Model II	Model I	Model II	Model I	Model II
k_{12}, hr.$^{-1}$	0.201	0.338	0.178	0.297	0.145	0.273	0.144	0.222
k_{21}, hr.$^{-1}$	0.101	0.060	0.160	0.097	0.058	0.030	0.049	0.033
k_{13}, hr.$^{-1}$	0.137	—	0.121	—	0.127	—	0.079	—
k_{22}, hr.$^{-1}$	—	0.041	—	0.065	—	0.027	—	0.017

Table II—Pharmacokinetic Profile of Coumermycin A_1 in Four Human Subjects (Model Independent Parameters)

Subject	A		B		C		D	
	Model I	Model II	Model I	Model II	Model I	Model II	Model I	Model II
Dose, mg.	50		50		100		100	
Body weight, kg.	64.0		82.7		97.8		54.1	
Dose, mg./kg.	0.78		0.61		1.02		1.85	
I.V. data								
α, hr.$^{-1}$	0.405		0.412		0.306		0.257	
corresponding $t^{1/2}$, hr.	1.71		1.68		2.26		2.69	
β, hr.$^{-1}$	0.034		0.047		0.024		0.015	
corresponding $t^{1/2}$, hr.	20.6		14.8		28.6		46.3	
A, mcg./ml.	15.84		9.82		31.85		28.03	
B, mcg./ml.	3.48		4.49		4.20		4.71	
Fraction of drug in central compartment, fc								
$= \beta/k_{13}$ or	0.25	—	0.39	—	0.19	—	0.19	—
$= 1 - \beta/k_{23}$	—	0.17	—	0.28	—	0.11	—	0.2
V_p = volume of central compartment, l.	2.6		3.5		2.8		3.1	
Oral data % of dose absorbed								
Calculated from area ratio (oral/i.v.)	16.9		12.7		15.2		28.4	
Calculated from kinetic constants	16.4	14.0	13.2	13.0	14.4	13.0	30.4	28.0
Amount of drug absorbed, mg.	8.3	7.7	6.5	6.4	14.8	14.1	29.4	28.2
% of absorbed dose absorbed at:								
1 hr.	7.4	8.7	4.9	5.0	6.6	7.3	10.0	10.9
2 hr.	31.7	37.0	25.7	25.9	19.1	21.1	26.5	28.8
3 hr.	50.8	59.3	49.8	50.2	38.5	42.5	53.6	58.2
4 hr.	61.4	71.6	71.6	72.2	52.5	58.1	64.7	70.3
6 hr.	80.9	94.4	94.2	94.7	72.3	80.1	80.1	86.9
8 hr.	85.9	100	100	100	75.0	83.0	83.9	90.8
24 hr.	98.3				94.0	94.4	100	100
Absorption rate, hr.$^{-1}$	0.278	0.394	0.402	0.408	0.249	0.314	0.311	0.344

of the models in that: Model I, $fc = \beta/k_{13}$ (7) or Model II, $fc = 1 - \beta/k_{23}$.

The values reported in Table II indicated that fc ranged from 0.19–0.39 (Model I) and 0.11–0.28 (Model II).

Absorption Characteristics—Orally administered coumermycin A_1 resulted in clinically effective blood levels. Fourteen percent of the administered dose was absorbed in three of the subjects and 28% in the fourth.

The extent of absorption was determined by two different procedures. In one, the areas under the oral and intravenous serum level curves were compared to yield a measure of availability. This method would be model independent. In the other, the kinetic constants and volume of Compartment I, V_p, were used for the calculation of the percent absorbed by utilizing the equation presented by Loo *et al.* (8) for Model I, and by modifying the equation of Loo *et al.* (8) for Model II. The derivation of the modified equation is presented in *Appendix II*. The data in Table II indicate that the estimates of oral availability were practically the same when calculated with either of the models resulting in an additional model independent parameter.

The percent available drug absorbed with time has been calculated for each subject and is also reported in Table II. The mean values indicate that approximately 8% of the absorbed dose was absorbed in 1 hr., 28% in 2 hr., 53% in 3 hr. and 89% in 6 hr. In each case the serum level peaks following oral administration of the drug appear to plateau during the 3–6-hr. interval.

SUMMARY

The pharmacokinetic profile of coumermycin A_1 has been determined for four subjects following intravenous and oral administration of the drug. The apparent elimination rate from the bloodstream is slow with a half-life range of 15–46 hr. In addition, there appears to be a tendency toward a decrease in elimination rate with an increase in mg./kg. dose. The slow elimination may result in a potential for prolonged therapeutic effectiveness. The distribution characteristics are such that the drug is initially confined to the small plasma water compartment following intravenous injection. The drug appears to be highly biotransformed inasmuch as no intact drug is detectable in the urine. However, alternate routes of excretion remain to be explored.

Following the oral administration of coumermycin A_1, 14% of the administered dose was absorbed in three of the subjects and 28% was absorbed in the fourth, with a mean percent of absorbed dose absorbed with time calculated to be 8% in 1 hr., 28% in 2 hr., 53% in 3 hr., and 89% in 6 hr.

The design of a pharmacokinetic model for coumermycin A_1 is discussed with emphasis on the meaning of the elimination rate constant, as defined by each of the models.

APPENDIX I: DETERMINATION OF KINETIC CONSTANTS

Model: Compartment 1 $\underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}}$ Compartment 2 $\xrightarrow{k_{23}}$ Compartment 3

where the amount in Compartment 1 = X_p and the amount in Compartment 2 = X_t, and k_{12}, k_{21}, and k_{23} are first-order rate constants.

The differential equations for the model are:

$$\frac{dX_p}{dt} = -k_{12}X_p + k_{21}X_t \qquad \text{(Eq. 1)}$$

$$\frac{dX_t}{dt} = k_{12}X_p - (k_{21} + k_{23})X_t \qquad \text{(Eq. 2)}$$

if $X_p = X^\circ$ (administered dose) and $X_t = 0$ at time = 0, Eq. 1 and 2 can be solved by Laplace transforms so that

$$\frac{X_p}{X^\circ} = \left[\frac{k - \alpha}{\beta - \alpha}\right] e^{-\alpha t} + \left[\frac{k - \beta}{\alpha - \beta}\right] e^{-\beta t} \qquad \text{(Eq. 3)}$$

where

$$k = k_{21} + k_{23} \qquad \text{(Eq. 4)}$$

$$\alpha\beta = k_{12}k_{23} \qquad \text{(Eq. 5)}$$

$$(\alpha + \beta) = k_{12} + k_{21} + k_{23} \qquad \text{(Eq. 6)}$$

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 7)}$$

so that

$$A = \frac{C_p^\circ(k - \alpha)}{\beta - \alpha} \qquad \text{(Eq. 8)}$$

and

$$B = \frac{C_p^\circ(k - \beta)}{\alpha - \beta} \qquad \text{(Eq. 9)}$$

where

$$C_p^\circ = A + B \qquad \text{(Eq. 10)}$$

Therefore, $$k = \frac{A\beta + B\alpha}{A + B} = k_{21} + k_{23} \quad \text{(Eq. 11)}$$

from Eq. 6, $$k_{12} = \alpha + \beta - k = \alpha + \beta - \frac{A\beta + B\alpha}{A + B} \quad \text{(Eq. 12)}$$

from Eq. 5, $$k_{23} = \frac{\alpha \cdot \beta}{k_{12}} \quad \text{(Eq. 13)}$$

and therefore from Eq. 6,

$$k_{21} = \alpha + \beta - k_{12} - k_{23} \quad \text{(Eq. 14)}$$

APPENDIX II: INTRINSIC ABSORPTION RATE CALCULATION

Model: Drug at absorption site $\rightsquigarrow$ Compartment 1 $\underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}}$ Compartment 2 $\downarrow k_{23}$ Compartment 3

where the mass balance equation indicates that the amount of drug absorbed at any time, in concentration units, is defined as:

$$\left(\frac{A}{V_p}\right)_{tn} = (C_p)_{tn} + (C_t)_{tn} + (C_{me})_{tn} \quad \text{(Eq. 1)}$$

The concentration in Compartment 1 $= C_p$, and the concentration in Compartment 2 $= C_t$, and k_{12}, k_{21} and k_{23} are the first-order rate constants.

The differential equation to express the rate of change of the tissue compartment with time is

$$\frac{d(C_t)_{tn}}{dt} = -k_{21}(C_t)_{tn} + k_{12}(C_p)_{tn} - k_{23}(C_t)_{tn} \quad \text{(Eq. 2)}$$

Since the blood level data between times t_{n-1} and t_n can be approximated by a straight line segment, we write

$$(C_p)_{tn} = (C_p)_{t_{n-1}} + M\tau \quad \text{(Eq. 3)}$$

where $\tau = t_n - t_{n-1}$; $\Delta C_p = (C_p)_{tn} - (C_p)_{t_{n-1}}$ and $M = \Delta C_p/\tau$. If we take t_{n-1} as an initial time, the Eq. 2 can be written as

$$\frac{d(C_t)_{tn}}{d\tau} = -k_{21}(C_t)_{tn} + k_{12}[(C_p)_{t_{n-1}} + M\tau] - k_{23}(C_t)_{tn} \quad \text{(Eq. 4)}$$

Let $K = k_{21} + k_{23}$.

Equation 4 can be solved by Laplace transformation with initial conditions $C_t(0) = (C_t)_{t_{n-1}}$. Rewriting Eq. 4 as

$$\frac{d(C_t)_{tn}}{dt} + K(C_t)_{tn} = k_{12}[(C_p)_{t_{n-1}} + M\tau)] \quad \text{(Eq. 5)}$$

and taking the Laplace transform of both sides, we obtain

$$S(\bar{C}_t)_{tn} - (C_t)_{t_{n-1}} + K(\bar{C}_t)_{tn} = k_{12}\left(\frac{(C_p)_{t_{n-1}}}{S} + \frac{M}{S^2}\right)$$

$$(S + K)(\bar{C}_t)_{tn} = (C_t)_{t_{n-1}} + k_{12}\left(\frac{(C_p)_{t_{n-1}}}{S} + \frac{M}{S^2}\right)$$

$$(\bar{C}_t)_{tn} = \frac{(C_t)_{t_{n-1}}}{(S + K)} + \frac{k_{12}(C_p)_{t_{n-1}}}{S(S + K)} + \frac{k_{12}M}{S^2(S + K)}$$

$$= \frac{(C_t)_{t_{n-1}}}{(S + K)} + \frac{k_{12}(C_p)_{t_{n-1}}}{K}\left(\frac{1}{S} - \frac{1}{S + K}\right) + k_{12}M\left(\frac{1/K}{S^2} - \frac{1/(K)^2}{S} + \frac{1/(K)^2}{(S + K)}\right) \quad \text{(Eq. 6)}$$

taking inverse Laplace transforms on both sides of equation

$$(C_t)_{tn} = L^{-1}[(C_t)_{tn}]$$

$$= (C_t)_{t_{n-1}}e^{-K\tau} + \frac{k_{12}(C_p)_{t_{n-1}}}{K}(1 - e^{-K\tau}) + \frac{k_{12}M}{(K)^2}[\tau(K) - 1 + e^{-K\tau}] \quad \text{(Eq. 7)}$$

or

$$(C_t)_{tn} = (C_t)_{t_{n-1}}e^{-K\tau} + \frac{k_{12}(C_p)_{t_{n-1}}}{K}(1 - e^{-K\tau}) + \frac{k_{12}M}{K^2}(K\tau + e^{-K\tau} - 1) \quad \text{(Eq. 8)}$$

The third term of Eq. 8 can be expanded in terms of a two term Taylor series:

$$\frac{k_{12}}{K^2}\left(\frac{C_p}{\tau}\right)\left[1 - K\tau - \left(1 - K\tau + \frac{K^2\tau^2}{2}\right)\right] = \frac{k_{12}}{K^2}\frac{\Delta C_p}{\tau}\frac{K^2(\tau)^2}{2} = -\frac{k_{12}\tau\Delta C_p}{2}$$

Then Eq. 8 becomes

$$(C_t)_{tn} = (C_t)_{t_{n-1}}e^{-K\tau} + \frac{k_{12}(C_p)_{t_{n-1}}}{K}(1 - e^{-K\tau}) + \frac{k_{12}\Delta C_p\tau}{2}$$

i.e.,

$$(C_t)_{tn} = (C_t)_{t_{n-1}}e^{-K\tau} + \frac{k_{12}(C_p)_{t_{n-1}}}{K}(1 - e^{-K\tau}) + \frac{k_{12}\Delta C_p\tau}{2} \quad \text{(Eq. 9)}$$

Using Eq. 9, we can calculate the amount metabolized C_{me} and excreted up to time t_n in concentration units:

$$(c_{me})_{tn} = k_{23}\int_{t_0}^{t_n}(C_t)_{tn}dt \quad \text{(Eq. 10)}$$

Therefore, the amount of drug absorbed at any time in concentration units results when Eqs. 9 and 10 are substituted into Eq. 1.

$$\left(\frac{A}{V_p}\right)_{tn} = (C_p)tn' + (C_t)_{t_{n-1}}e^{-(K\tau)} + \frac{k_{12}(C_p)_{tn-1}}{K}(1 - e^{-K\tau}) + \frac{k_{12}\Delta C_p\tau}{2} + k_{23}\int_{t_0}^{t_n}(C_t)_{tn}d_t \quad \text{(Eq. 11)}$$

Eq. 11 has been programmed for computation on the GE 265 time sharing system. The slope of the percent remaining to be absorbed *versus* time plot provides the absorption rate constant of the drug.

REFERENCES

(1) E. Grunberg and M. Bennett, *Antimicrobial Agents Chemotherapy*, **1965**, p. 786.

(2) J. Berger, A. J. Schocher, A. D. Batcho, B. Pecherer, O. Keller, J. Maricq, A. E. Karr, B. P. Vaterlaus, A. Furlenmeier, and H. Spiegelberg, *ibid.*, **1965**, p. 778.

(3) H. Solomon, unpublished data on file, Hoffmann-La Roche, Nutley, N. J., 1968.

(4) J. Unowsky and M. Douglas, unpublished data on file, Hoffmann-La Roche, Nutley, N. J., 1968.

(5) S. Riegelman, J. C. K. Loo, and M. Rowland, *J. Pharm. Sci.*, **57**, 117(1968).

(6) R. Nagashima, G. Levy, and R. A. O'Reilly, *ibid.*, **57**, 1888 (1968).

(7) M. Gibaldi, R. Nagashima, and G. Levy, *ibid.*, to be published.

(8) J. C. K. Loo and S. Riegelman, *ibid.*, **57**, 918(1968).

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