to that of indomethacin and they were without effect on the chronic inflammatory state induced by the mycobacterium adjuvant. No apparent structure-activity relationships could be deduced from the above studies.

REFERENCES

(1) O'Brien, J. E., and Thoms, R. K., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 258(1958).
(2) von Kaulla, K. N., *J. Med. Chem.*, **8**, 164(1965).
(3) Rader, R. W., and Wulf, R. J., *Federation Proc.*, **25**, 498(1966).
(4) Wulf, R. J., School of Pharmacy, University of Connecticut, Storrs, Conn., personal communication, 1967.
(5) Malone, M. H., and Robichaud, R. C., *Lloydia*, **25**, 320(1962).
(6) Cooper, D. J., Miya, T. S., and Edwards, L. D., *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 163(1956).
(7) Beck, L. V., Rieck, V. D., and Duncan, B., *Proc. Soc. Expll. Biol. Med.*, **97**, 229(1958).
(8) Benesch, R., and Benesch, R. E., *Arch. Biochem.*, **19**, 35(1948).
(9) Benesch, R. E., and Benesch, R., *ibid.*, **28**, 43(1950).
(10) Kolthoff, I. M., and Harris, W. E., *Ind. Eng. Chem., Anal. Ed.*, **18**, 161(1946).
(11) Winter, C. A., Risley, E. A., and Nuss, G. W., *Proc. Soc. Expll. Biol. Med.*, **111**, 544(1962).
(12) Harris, J. M., and Spencer, P. S. J., *J. Pharm. Pharmacol.*, **14**, 464(1962).
(13) Duncan, D. B., *Biometrics*, **11**, 1(1955).
(14) Nuss, G. W., Merck Inst. for Therap. Res., West Point, Pa., personal communication, 1965.
(15) Kaplan, H. R., Wolke, R. E., and Malone, M. H., *J. Pharm. Sci.*, **56**, 1385(1967).
(16) Newbould, B. B., *Brit. J. Pharmacol.*, **21**, 127(1963).
(17) Smith, D. L., D'Amour, M. C., and D'Amour, F. E., *J. Pharmacol. Expll. Therap.*, **77**, 184(1943).
(18) Takesue, E. I., and Miya, T. S., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 19(1957).
(19) Register, V. D., and Bartlett, R. G., Jr., *J. Biol. Chem.*, **212**, 741(1955).
(20) Krimsky, I., and Racker, E., *ibid.*, **198**, 721(1952).

Keyphrases

Thymotic acid and homologs—activity
Analgesia rat tail flick method
Antiphlogistic activity—pedal carrageenin injection
Anti-inflammatory activity-*Mycobacterium butyricum* cell injection.
Hepatic glutathione depletion—hind leg tourniquet

Lag Time Before Essentially Constant Urinary Excretion Rate Is Attained

By JOHN G. WAGNER and JACK I. NORTHAM

If a substance is continuously infused intravenously at a constant rate, the plasma concentration will increase until it reaches an asymptotic concentration. If the urinary excretion rate of the substance is directly proportional to its plasma concentration, the urinary excretion rate will become essentially constant as the asymptotic plasma concentration is approached. Analogously, if a metabolite is formed at a constant rate, due to saturation of an enzyme system metabolizing the drug, the plasma concentration of the metabolite would be expected to approac hsome asymptotic concentration. If the urinary excretion rate of the metabolite is directly proportional to its plasma concentration, the urinary excretion rate of the metabolite would become essentially constant as the asymptotic plasma concentration is approached. Equations were derived to estimate the lag time between initiation of the maintained constant input rate to the plasma compartment and the time when, for all practical purposes, the asymptotic plasma concentration and the constant urinary excretion rate may be considered to have been reached for both the one- and two-compartment open models. The theoretical expectation is that, if the cumulative excretion curve is nearly linear, then there must be an appreciable negative intercept when the line is extrapolated back to zero time. It is theoretically impossible for a cumulative urinary excretion curve to be linear and the line extrapolate through the origin corresponding to zero excretion at zero time.

IF A SUBSTANCE is continuously infused intravenously at a constant rate the blood (serum or plasma) concentration will increase until it reaches an asymptotic value (1). However, as the curves of Rescigno and Segre (1) and Wagner and Nelson (2) illustrate, it requires an appreciable time to approach the asymptotic concentration. If the urinary excretion rate of the substance is directly proportional to its plasma concentration, then the urinary excretion rate will become essentially constant, and the cumulative urinary excretion curve will become essentially linear, as the asymptotic plasma concentration is approached.

Analogously, if a metabolite is formed at a constant rate, due to saturation of the enzyme system metabolizing the drug, the plasma concentration of the metabolite would be expected to approach some asymptotic value,

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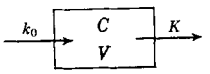
after a certain time. If the urinary excretion rate of the metabolite is directly proportional to its plasma concentration, then the urinary excretion rate of the metabolite will become essentially constant, and the cumulative urinary excretion curve will become essentially linear, as the asymptotic plasma concentration of the metabolite is approached. In the case of a metabolite some finite additional time would also be required for absorption of the drug and build up of blood concentration of unchanged drug which would be necessary before an enzyme system couid become saturated. This additional time would have to be added to the lag time between initiation of the constant (zero-order) formation rate and the time the asymptotic plasma concentration is approached, to estimate the total time required for the cumulative urinary excretion curve to become essentially linear.

The two most common pharmacokinetic models, which apply to the above situations, are the one- and two-compartment open models. One purpose of this report is to show how one may estimate for these models the time lag necessary between the start of the zero-order input into the plasma compartment and the time when, for all practical purposes, the asymptotic plasma concentration and the constant urinary excretion rate is attained. Another purpose is to show how the maximum excretion rate may be estimated before it is attained if the rate constant for elimination is known.

EXPERIMENTAL

One-Compartment Open Model

Intravenous Infusion at a Constant Rate—The model is shown in Scheme I. Here k_0 is the constant (zero-order) infusion rate with dimensions mass/time, V is the apparent volume of distribution, and C is the plasma concentration of the substance infused at time t, and K is the first-order rate constant for elimination by all processes. For this model the appropriate classical equation *during the infusion* is:



Scheme I

$$C = \frac{k_0}{VK}(1 - e^{-Kt}) \qquad \text{(Eq. 1)}$$

where t is the time from the start of the infusion. If urinary excretion rate is directly proportional to plasma concentration, then

$$dA_u/dt = fVKC \qquad \text{(Eq. 2)}$$

where dA_u/dt is the urinary excretion rate and f is the fraction of substance reaching the plasma compartment which is ultimately excreted in the urine. Substitution of Eq. 1 into Eq. 2 and simplifying gives

$$dA_u/dt = fk_0(1 - e^{-Kt}) \qquad \text{(Eq. 3)}$$

Let t_a be the time that the excretion rate reaches some proportion, p, of the maximum rate, fk_0. Then,

$$dA_u/dt = p.f.k_0 \qquad \text{(Eq. 4)}$$

when

$$e^{-Kt_a} = 1 - p \qquad \text{(Eq. 5)}$$

Taking logarithms of both sides of Eq. 5 we find

$$t_a \simeq 3/K \qquad \text{when } p = 0.95 \qquad \text{(Eq. 6)}$$

$$t_a \simeq 4.6/K \qquad \text{when } p = 0.99 \qquad \text{(Eq. 7)}$$

If one substitutes $\ln 2/t_{1/2}$ for K, where $t_{1/2}$ is the half-life, into Eq. 5, takes logarithms, and rearranges, one finds

$$t_a = -1.443 \ln (1 - p) \cdot t_{1/2} \qquad \text{(Eq. 8)}$$

Hence,

$$t_a/t_{1/2} = 4.322 \qquad \text{when } p = 0.95 \qquad \text{(Eq. 9)}$$

and,

$$t_a/t_{1/2} = 6.645 \qquad \text{when } p = 0.99 \qquad \text{(Eq. 10)}$$

Hence, the time, t_a, for the excretion rate to reach the same proportion, p, of the maximum rate, fk_0, and the plasma concentration to reach the same proportion, p, of the asymptotic value, k_0/VK, is directly proportional to the half-life of elimination if the one-compartment open model applies.

Integration of Eq. 3 yields

$$A_u = fk_0\left[t - \left(\frac{1 - e^{-Kt}}{K}\right)\right] \qquad \text{(Eq. 11)}$$

where A_u is the cumulative amount excreted in the urine to time t. Substitution of values for f, k_0, K, and various t values would yield a curve of A_u *versus* t by application of Eq. 11. If one chose two points, $(A_u^{T_2}, T_2)$ and $(A_u^{T_1}, T_1)$, on this curve, joined them with a straight line, then extrapolated the line back to time zero corresponding to an intercept $(A_u)_{t=0}$, then the slope, $\Delta A_u/\Delta t$, of the line may be shown to be

$$\frac{\Delta A_u}{\Delta t} = fk_0\left[1 - \left\{\frac{e^{-KT_1} - e^{-KT_2}}{K(T_2 - T_1)}\right\}\right] \qquad \text{(Eq. 12)}$$

The value of the intercept may be shown to be:

$$(A_u)_{t=0} = \frac{fk_0}{K}\left[\left(\frac{T_2e^{-KT_1} - T_1e^{-KT_2}}{T_2 - T_1}\right) - 1\right] \qquad \text{(Eq. 13)}$$

The equation of such a line will be:

$$\hat{A}_u = \left(\frac{\Delta A_u}{\Delta t}\right)t - (A_u)_{t=0} \qquad \text{(Eq. 14)}$$

The line will cross the time axis when $\hat{A}_u = 0$ at a point, $t_{(A_{u=0})}$, given by

$$t_{(A_{u=0})} = \frac{(T_2 - T_1) - (T_2e^{-KT_1} - T_1e^{-KT_2})}{K(T_2 - T_1) - (e^{-KT_1} - e^{-KT_2})} \qquad \text{(Eq. 15)}$$

Utilizing Eqs. 12 through 15 we can show that

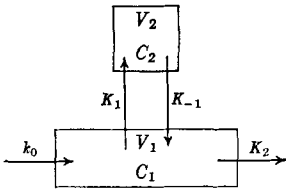
$$k_0 = \frac{(A_u)_{t=0}}{t_{(A_u=0)}\left[1 - \left\{\frac{e^{-KT_1} - e^{-KT_2}}{K(T_2 - T_1)}\right\}\right]} \quad \text{(Eq. 16)}$$

Hence, if an estimate of K is available, one may estimate the maximum excretion rate, fk_0, even from a markedly curved segment of the cumulative excretion plot.[1]

Metabolite Formation at a Constant Rate—If a metabolite is formed at a constant rate, then Scheme I may apply but the symbols have to be redefined. In this case k_0 would be the constant formation rate, V would be the volume of distribution, C the plasma concentration of the metabolite at time t, and K would be the first-order rate constant for elimination of the metabolite by all processes. If the metabolite was completely excreted in the urine (*i.e.*, $f = 1$), then K would be the first-order rate constant for urinary excretion of the metabolite. The same equations as above would apply.

Two-Compartment Open Model

Intravenous Infusion at a Constant Rate—The model is shown in Scheme II.



Scheme II

Here k_0 is the constant (zero-order) infusion rate with dimension mass/time; K_2 is the first-order rate constant for elimination of the substance infused by all processes; V_1 is the volume of the inner (plasma) compartment; and C_1 is the concentration of the substance infused in this compartment at time t; V_2 is the volume of the outer compartment, and C_2 is the concentration of the substance infused in this compartment at time t; K_1 is a first-order rate constant representing the instantaneous fraction of substance in the inner compartment being transferred to the outer compartment; and $K_{-1} = (V_1/V_2)K_1 = VK_1$, where $V = V_1/V_2$.

The solutions of the appropriate differential equations for this model were given by Gaudino (3). Rewritten in the nomenclature of Wagner and Northam (4) the equation for the concentration, C_1, is:

$$C_1 = \frac{k_0}{V_1K_2}\left[1 - \left(\frac{K_2 - \beta}{\alpha - \beta}\right)e^{-\alpha t} + \left(\frac{K_2 - \alpha}{\alpha - \beta}\right)e^{-\beta t}\right] \quad \text{(Eq. 17)}$$

where

$$\alpha = {}^1/_2[(K_1 + K_2 + K_{-1}) + \sqrt{(K_1 + K_2 + K_{-1})^2 - 4K_{-1}K_2}] \quad \text{(Eq. 18)}$$

[1] One may also estimate fk_0 with only one point on the curve by use of Eq. 11.

$$\beta = {}^1/_2[(K_1 + K_2 + K_{-1}) - \sqrt{(K_1 + K_2 + K_{-1})^2 - 4K_{-1}K_2}] \quad \text{(Eq. 19)}$$

If D is the total dose infused and T is the infusion time, then

$$k_0 = D/T \quad \text{(Eq. 20)}$$

It should be noted that $\alpha > \beta$, and Eq. 17 only applies when $t < T$. If urinary excretion rate is directly proportional to the concentration C_1, then:

$$dA_u/dt = fV_1K_2C_1 \quad \text{(Eq. 21)}$$

Substitution of Eq. 17 into Eq. 21 and simplifying yields

$$dA_u/dt = fk_0\left[1 - \left(\frac{K_2 - \beta}{\alpha - \beta}\right)e^{-\alpha t} + \left(\frac{K_2 - \alpha}{\alpha - \beta}\right)e^{-\beta t}\right] \quad \text{(Eq. 22)}$$

If t_a is the time required for the excretion rate to reach some proportion, p, of the maximum rate, fk_0, then

$$dA_u/dt = p.f.k_0 \quad \text{(Eq. 23)}$$

when

$$\left(\frac{K_2 - \beta}{\alpha - \beta}\right)e^{-\alpha t_a} - \left(\frac{K_2 - \alpha}{\alpha - \beta}\right)e^{-\beta t_a} = 1 - p \quad \text{(Eq. 24)}$$

Division by K_2 in Eq. 24 yields

$$(1 - \beta/K_2)e^{-\alpha/K_2(K_2t_a)} - (1 - \alpha/K_2)e^{-\beta/K_2(K_2t_a)} - (1 - p)\left(\frac{\alpha}{K_2} - \frac{\beta}{K_2}\right) = 0 \quad \text{(Eq. 25)}$$

For given V_1/V_2 and K_1/K_2 ratios, α/K_2 and β/K_2 remain constant, so that for a given p, the value of K_2t_a is unique. Based on Eqs. 18, 19, and 25 a digital computer program was written which allowed print-out of t_a and $t_a/t_{1/2}$, where $t_{1/2} = \ln 2/K_2$, for given values of V_1/V_2, K_1/K_2, K_2, and p. For $p = 0.95$ and 0.99, $K_1/K_2 = 0.1$, 0.25, 0.5, 1, 2, 5, 10, and 100 and $V_1/V_2 = 0.125$, 0.25, 0.5, 1, 2, 4, and 8, values of $t_a/t_{1/2}$ were estimated. Hence 112 values of $t_a/t_{1/2}$ were calculated and these values served as the basis for Figs. 1 and 2.

Integration of Eq. 22 yields

$$A_u = fk_0\left[t - \frac{(K_2 - \beta)}{\alpha(\alpha - \beta)}(1 - e^{-\alpha t}) + \frac{(K_2 - \alpha)}{\beta(\alpha - \beta)}(1 - e^{-\beta t})\right] \quad \text{(Eq. 26)}$$

One may plot a curve of A_u *versus* t by substituting appropriate values into Eq. 26. If one chose two points, $(A_u{}^{T_2}, T_2)$ and $(A_u{}^{T_1}, T_1)$, on this curve, joined them with a straight line, then extrapolated the line back to zero corresponding to the intercept, $(A_u)_{t=0}$, then the slope, $\Delta A_u/\Delta t$, of the line may be shown to be

$$\Delta A_u/\Delta t = fk_0\left[1 - \frac{1}{T_2 - T_1}\left\{\frac{K_2 - \beta}{\alpha(\alpha - \beta)}(e^{-\alpha T_1} - e^{-\alpha T_2}) - \frac{K_2 - \alpha}{\beta(\alpha - \beta)}(e^{-\beta T_1} - e^{-\beta T_2})\right\}\right] \quad \text{(Eq. 27)}$$

The value of the intercept may be shown to be

$$(A_u)_{t=0} = fk_0\left[\left(\frac{V+1}{V}\right)\left(\frac{1}{K_2}\right) - \frac{K_2-\beta}{\alpha(\alpha-\beta)}\left\{e^{-\alpha T_2} + \frac{T_2}{T_2-T_1}(e^{-\alpha T_1} - e^{-\alpha T_2})\right\} + \frac{K_2-\alpha}{\beta(\alpha-\beta)}\left\{e^{-\beta T_2} + \frac{T_2}{T_2-T_1}(e^{-\beta T_1} - e^{-\beta T_2})\right\}\right] \quad \text{(Eq. 28)}$$

The equation of the line is as given by Eq. 14 except the slope and intercept are defined by Eqs. 27 and 28. The line will cross the time axis at a point, $t(A_{u=0})$, given by

$$t(A_{u=0}) = \frac{\left(\frac{V+1}{V}\right)\left(\frac{1}{K_2}\right) - \frac{K_2-\beta}{\alpha(\alpha-\beta)}\left\{e^{-\alpha T_2} + \frac{T_2}{T_2-T_1}(e^{-\alpha T_1} - e^{-\alpha T_1})\right\} + \frac{K_2-\alpha}{\beta(\alpha-\beta)}\left\{e^{-\beta T_2} + \frac{T_2}{T_2-T_1} \times (e^{-\beta T_1} - e^{-\beta T_2})\right\}}{1 - \frac{1}{T_2-T_1}\left\{\frac{K_2-\beta}{\alpha(\alpha-\beta)}(e^{-\alpha T_1} - e^{-\alpha T_2}) - \frac{K_2-\alpha}{\beta(\alpha-\beta)}(e^{-\beta T_1} - e^{-\beta T_2})\right\}} \quad \text{(Eq. 29)}$$

Utilizing Eqs. 27 through 29 one can show that

$$fk_0 = \frac{(A_u)_{t=0}}{t(A_{u=0})\left[1 - \frac{1}{T_2-T_1}\left\{\frac{K_2-\beta}{\alpha(\alpha-\beta)}(e^{-\alpha T_1} - e^{-\alpha T_2}) - \frac{K_2-\alpha}{\beta(\alpha-\beta)}(e^{-\beta T_1} - e^{-\beta T_2})\right\}\right]} \quad \text{(Eq. 30)}$$

It should be noted that as T_1 and T_2 become large then

$$(A_u)_{t=0} \to fk_0\left(\frac{V+1}{V}\right)\left(\frac{1}{K_2}\right), \quad t(A_{u=0}) \to \left(\frac{V+1}{V}\right)\left(\frac{1}{K_2}\right), \Delta A_u/\Delta t \to fk_0$$

and

$$fk_0 \to (A_u)_{t=0}/t(A_{u=0})$$

Metabolite Formation at a Constant Rate—If a metabolite is formed at a constant rate, then Scheme II may apply but the symbols have to be redefined. In the metabolite case, k_0 would be the constant formation rate and K_2 would be the first-order rate constant for elimination of metabolite by all processes. If the metabolite was completely excreted in the urine (*i.e.*, $f = 1$), then K_2 would be the first-order rate constant for urinary excretion of the metabolite, V_1 would be the volume of the inner compartment, C_1 the concentration of metabolite in this compartment at time t; V_2 would be the volume of the outer compartment, and C_2 the concentration of metabolite in this compartment at time t. K_1, K_{-1}, and f would have the same significance except the reference to metabolite rather than unchanged drug. Then Eqs. 17 through 30 would apply.

RESULTS

Table I gives values of the lag time, t_a, corresponding to different half-lives and rate constants for the one-compartment open model. The lag times listed were calculated with Eqs. 9 and 10.

Figures 1 and 2 are plots of the ratio $t_a/t_{1/2}$ *versus* K_1/K_2 on log-log scales for the two-compartment open model. Here $t_{1/2}$ is the half-life of elimination estimated from K_2 (*i.e.*, $t_{1/2} = \ln 2/K_2$). Figure 1 gives values of $t_a/t_{1/2}$ when $p = 0.95$, and Fig. 2 gives value of $t_a/t_{1/2}$ when $p = 0.99$. The values of t_a were estimated with an appropriate digital computer program based on Eqs. 18, 19, and 25.

Figure 3 has two examples illustrating use of Eqs. 11 through 16. Letting fk_0 be 1 unit/hr. and K be 1.0 hr.$^{-1}$, values of A_u corresponding to t = 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, and 4.6 hr. were calculated using Eq. 11; these correspond to the circled points in Fig. 3. Letting T_1 = 1.5 hr. and T_2 = 3.0 hr., a straight line was drawn joining the ($A_u{}^{T_2}$, T_2) and ($A_u{}^{T_1}$,T_1) points and the line extrapolated back to zero time; the equation of this line is $\hat{A}_u = 0.8845t - 0.6037$ corresponding to Eq. 14. Hence this line intersects the ordinate at $(A_u)_{t=0} = -0.6037$ and it crosses the time axis at the point $t(A_{u=0}) = 0.6825$ hr. The slope, $\Delta A_u/\Delta t$, estimated from these points, is 0.8845 indicating the excretion rate has reached only 88.45% of its maximum value. Using Eq. 16, however, the true maximum excretion rate of unity may be estimated. Letting T_1 = 3.0 hr. and T_2 = 4.6 hr., another straight line was drawn joining the points corresponding to these times, and the line was extrapolated back to the ordinate; the equation of this line is $\hat{A}_u = 0.9752t$

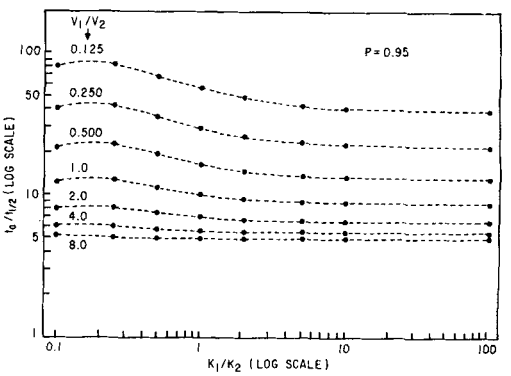


Fig. 1—Plot of the ratio $t_a/t_{1/2}$ versus *the ratio* K_1/K_2 *on a log-log scale for the two-compartment open model when* p = 0.95.

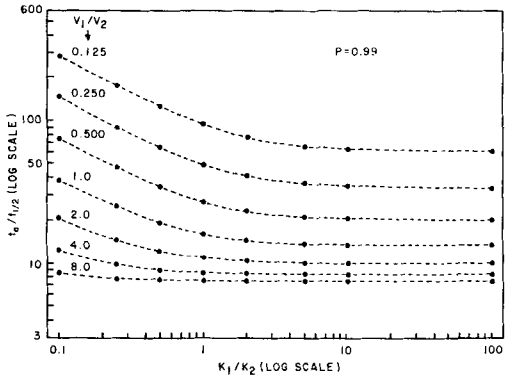


Fig. 2—Plot of the ratio $t_a/t_{1/2}$ *versus the ratio* K_1/K_2 *on a log-log scale for the two-compartment open model when* p = *0.99.*

— 0.8758 corresponding to Eq. 14. Hence this second line intersects the ordinate at $(A_u)_{t=0}$ = −0.8758 and it crosses the time axis at the point $t(A_{u=0})$ = 0.8981 hr. The slope, $\Delta A_u/\Delta t$, estimated from these points, is 0.9752 indicating that the excretion rate has reached 97.5% of its maximum value. Using Eq. 16 the time maximum excretion rate of unity may be estimated.

Figure 4 has two examples illustrating use of Eqs. 26 through 30. Letting fk_0 = 1 unit/hr., K_2 = 1 hr.$^{-1}$, K_1 = 5 hr.$^{-1}$, and V_1/V_2 = 2, use of Eqs. 18, 19, and 26 allowed calculation of the plotted points in the figure corresponding to the same times as in the one-compartment case. A straight line was drawn joining the points corresponding to 1.5 and 3.0 hr. and the line was extrapolated back to time zero; this line has the equation $\hat{A}_u$ = 0.7606 t − 0.5965. This line intersects the ordinate at $(A_u)_{t=0}$ = −0.5965 and it crosses the time axis at the point $t(A_{u=0})$ = 1.153 hr. The slope, $\Delta A_u/\Delta t$, estimated from these points, is 0.7606 indicating that the excretion rate has reached 76.06% of its maximum value. Using Eq. 30, however, the true maximum excretion rate of unity was estimated. A second straight line was drawn joining the points corresponding to 3.0 and 4.6 hr. and the line was extrapolated back to time zero; this line has the equation $\hat{A}_u$ = 0.9124t − 1.0518. This second line intersects the ordinate at $(A_u)_{t=0}$ = −1.0518 and it

TABLE I—VALUES OF THE LAG TIME, t_a, CORRESPONDING TO DIFFERENT HALF-LIVES, AND RATE CONSTANTS FOR THE ONE-COMPARTMENT OPEN MODEL

Half-Life, hr.	Rate Constant (K), hr.$^{-1}$	t_a, hr. p = 0.95[a]	t_a, hr. p = 0.99[b]
0.231	3.0	1.0	1.5
0.3465	2.0	1.5	2.3
0.693	1.0	3.0	4.6
1.386	0.5	6.0	9.2
2.77	0.25	12.0	18.4
4.62	0.15	20.0	31.0
6.93	0.10	30.0	46.0
13.86	0.05	60.0	92.0
69.3	0.01	300.0	460.0

[a] Values in this column calculated with Eq. 9. [b] Values in this column calculated with Eq. 10.

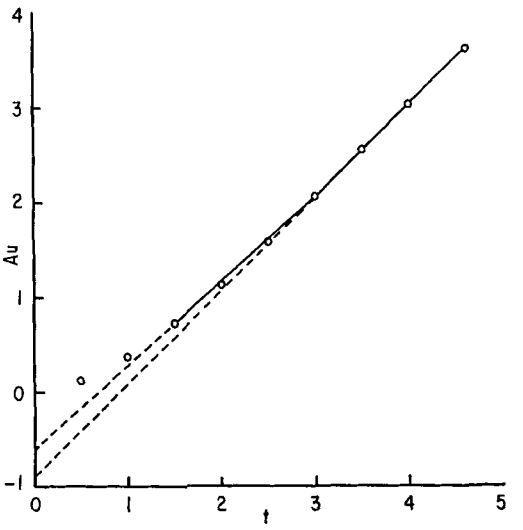


Fig. 3—Plot of the cumulative amount excreted in the urine (A_u) *against time* (t) *in hours for the one-compartment open model where* K = *1 hr.*$^{-1}$ *and* fk_0 = *1 unit/hr. The line joining the 1.5- and 3.0-hr. point has the equation* $\hat{A}_u$ = *0.8845*t − *0.6037; for this line* $(A_u)t_{=0}$ = −*0.6037,* $t(A_{u=0})$ = *0.6825 hr. and* $\Delta A_u/\Delta t$ = *0.8845. The line joining the 3.0- and 4.6-hr. points has the equation* $\hat{A}_u$ = *0.9752t* − *0.8758; for this line* $(A_u)t_{=0}$ = −*0.8758,* $t(A_{u=0})$ = *0.8981 hr. and* $\Delta A_u/\Delta t$ = *0.9752.*

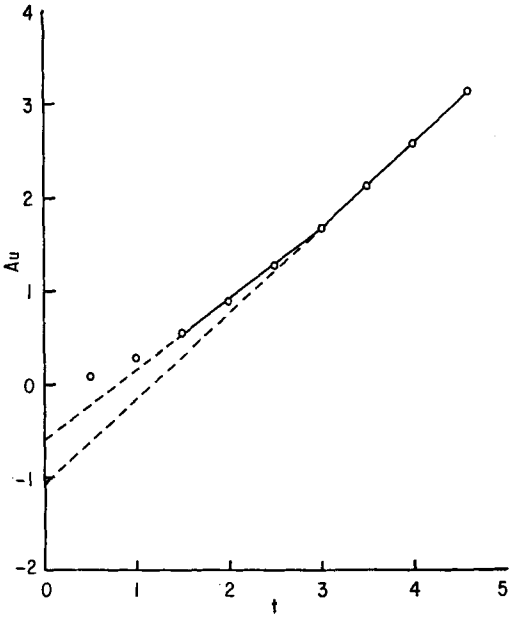


Fig. 4—Plot of the cumulative amount excreted in the urine (A_u) *against time* (t) *in hours for the two-compartment open model where* K_1 = *5 hr.*$^{-1}$, K_2 = *1 hr.*$^{-1}$, V_1/V_2 = *2, and* fk_0 = *1 unit/hr. The line joining the 1.5- and 3.0-hr. points has the equation* $\hat{A}_u$ = *0.7606*t − *0.5965; for this line* $(A_u)t_{=0}$ = −*0.5965,* $t(A_{u=0})$ = *0.7842 hr. and* $\Delta A_u/\Delta t$ = *0.7606. The line joining the 3.0- and 4.6-hr. points has the equation* $\hat{A}_u$ = *0.9124*t − *1.0518; for this line* $(A_u)t_{=0}$ = −*1.0518,* $t(A_{u=0})$ = *1.153 hr., and* $\Delta A_u/\Delta t$ = *0.9124.*

crosses the time axis at the point $t(A_{u=0}) = 1.153$ hr. The slope of 0.9124 indicates the excretion rate has reached 91.24% of its maximum value. Using Eq. 30 the true maximum excretion rate of unity may be estimated.

DISCUSSION

Cummings and Martin (5, 6) advanced theoretical considerations suggesting that the first-order rate constant for urinary excretion of a metabolite will not exceed 3 hr.$^{-1}$ and that it will probably not exceed 1 hr.$^{-1}$, even if the metabolite exhibits the maximum renal clearance. In light of this a maximum value of $K = 3$ hr.$^{-1}$ was used in Table I, and a value of $K = 1$ hr.$^{-1}$ was used in constructing Fig. 3 for the one-compartment open model. Analogously, a value of $K_2 = 1$ hr.$^{-1}$ was used in constructing Fig. 4 pertaining to the two-compartment open model.

Although an observed cumulative urinary excretion curve may *appear* linear before the theoretically required lag time for a given half-life of elimination, it would be wise to use the equations and figures in this report as a guide to the expectation of linearity of such curves. Cumulative urinary excretion curves are extremely insensitive indicators (2, 7–9). The excretion rate time plot, corresponding to the cumulative plot, should always be drawn also (7, 9). One would be unwise to infer constant formation rate of a metabolite, for example, unless the excretion rate time plot indicated an essentially maximum sustained rate *which commenced after some lag time* estimated by Eqs. 8 or 24.

Analogously, if all the drug administered in a dosage form is suspected of being absorbed at a constant rate, then the same consideration would apply as discussed here for constant-rate intravenous infusion. In such a case one would not expect the plasma concentration to plateau, nor the urinary excretion rate to become nearly constant, until the drug had been released and absorbed at a constant rate for a period of time which may be estimated by means of Eqs. 8 or 24. Since gastrointestinal transit time past the absorbing surface area is limited, and since this period of time is near or less than the lag time, t_a, for most drugs predicted by the equations in this report, it would be a rare event for constant-rate absorption to lead to a constant blood level or a constant urinary excretion rate after a single dose of drug in such a dosage form. For example, assume the one-compartment open model applies to the drug. If the half-life of elimination is 2.77 hr., corresponding to a rate constant of 0.25 hr.$^{-1}$, it would require about 12 hr. to reach 95% of the asymptotic plasma concentration and about 28 hr. to reach 99% of the asymptotic plasma concentration if the drug entered the blood at a constant rate. Gastrointestinal transit times *at the absorbing surface area* are usually of this order of magnitude or less.

If a metabolite is formed at a constant rate, due to saturation of an enzyme system metabolizing the drug, the above considerations indicate that it is theoretically impossible for the plot giving the cumulative urinary excretion of the metabolite as a function of time to be linear *and* the line extrapolate through the origin corresponding to zero excretion at zero time.

It should be noted that $t_a/t_{1/2}$ for the two-compartment open model is always greater than the corresponding value for the one-compartment open model for a given p value and when $0.125 \leq V_1/V_2 \leq 8$ and $0.1 \leq K_1/K_2 \leq 100$. Also, for given values of p and K_1/K_2, $t_a/t_{1/2}$ increases as V_1/V_2 decreases for the two-compartment open model. The examples shown in Figs. 3 and 4 are illustrative of the situation with very polar metabolites and drugs with short half-lives since a rate constant of 1 hr.$^{-1}$, corresponding to a half-life of 0.693 hr., was used in their construction. If the half-life of elimination is greater, the time scale on comparable plots would become greater. For example, Table I indicates that if the half-life of elimination is 6.93 hr. and the one-compartment model applies, then it would require 30 hr. to reach 95% of the maximum excretion rate if there was zero-order input to the blood; it would require greater than 30 hr. if the two-compartment open model applied.

CONCLUSIONS

The theoretical expectation is that if the cumulative urinary excretion curve is essentially linear, due to zero-order rate of formation of a metabolite or constant-rate intravenous infusion, then there must be an appreciable negative intercept when the linear portion is extrapolated back to zero time.[2] It is theoretically impossible for a cumulative urinary excretion curve to be linear *and* the line extrapolate through the origin corresponding to zero excretion at zero time.

[2] Proof of this for both the one- and two-compartment open models has been provided. Intuitively, one would expect the conclusions to hold for any compartment model.

REFERENCES

(1) Rescigno, A., and Segre, G., "Drug and Tracer Kinetics," Blaisdell Publishing Co., Waltham, Mass., 1966, pp. 32–35.
(2) Wagner, J. G., and Nelson, E., *J. Pharm. Sci.*, **53**, 1392(1964).
(3) Gaudino, M., *Proc. Soc. Exptl. Biol. Med.*, **70**, 672 (1949).
(4) Wagner, J. G., and Northam, J. I., *J. Pharm. Sci.*, **56**, 529(1967).
(5) Cummings, A. J., and Martin, B. K., *Nature*, **200**, 1296(1963).
(6) Cummings, A. J., Martin, B. K., and Park, G. S., *Brit. J. Pharmacol.*, **29**, 136(1967).
(7) Wagner, J. G., *J. Pharm. Sci.*, **52**, 1097(1963).
(8) *Ibid.*, **56**, 586(1967).
(9) Martin, B. K., *Brit. J. Pharmacol.*, **29**, 181(1967).

Keyphrases

Urinary excretion rates
Lag time—constant urinary excretion rate
Compartment models, open—one, two
Kinetic equations—zero-order plasma input, estimated maximum excretion
IV infusion—constant rate
Metabolite formation—constant rate