Multiple-Dosing Drug Kinetics: Nomographic Method of Estimating the Number of Doses Needed to Approach within a Fixed Percent of Asymptotic Minimum Drug Level

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Abstract □ Under multiple-dosing conditions, where a drug disappears from a compartment in an apparent monoexponential manner after each dose administration, equations can be derived which permit the calculation of the number of doses needed to approach within a predetermined fixed percent of the asymptotic minimum drug level in the compartment. Nomograms are presented which illustrate how these equations can be used in dosing calculations.

Keyphrases □ Kinetics—multiple-dosing drugs □ Dosing calculations—asymptotic minimum drug level □ Nomographic method—multiple-dosing kinetics

In recent years a number of authors (1–9) have been concerned with the mathematics of designing optimal drug dosing regimens whereby initial and constant maintenance doses are administered to achieve compartment levels of the drug resulting in an oscillation between some maximum and minimum limiting values under steady-state conditions. This steady-state condition or plateau effect occurs when the input of drug to the compartment is equal to the output of drug from the same compartment in a given dosing time interval. Such drug dosing calculations are most useful when an empirical relationship has been found between the amount or concentration of drug in a given compartment and the intensity of a particular pharmacological response at a given time.

One problem with using the proposed drug dosing regimen calculations is that it is often tedious to estimate how many maintenance doses are required to reach the steady-state condition. From a mathematical point of view, with certain ratios of initial to maintenance doses and biological half-life to dosing time intervals, an infinite number of maintenance doses are required to achieve steady-state conditions. From a practical point of view, it is usually not necessary to reach steady-state conditions *exactly* in order to elicit the desired pharmacological response from the proposed drug dosing regimen. It is sufficient in a great many cases to approach the steady-state conditions within a small predetermined percent of the asymptotic values. How close the actual drug amounts or concentrations in the compartment should be to the theoretically calculated asymptotic values in order to elicit the desired pharmacologic response depends upon answers to at least three questions.

How sensitive is the pharmacological response to changes in drug amounts or concentrations in the compartment at particular times during the multiple-dosing regimen? How sensitive are the analytical techniques used in detecting changes in drug amounts or concentrations in the fluids present in the compartment studied? And how reproducible is the apparent biological half-life measured in the same compartment when the drug is administered at widely spaced times or under frequent dosing conditions?

The purpose of this article is to derive equations from which nomograms can be constructed to permit an estimate of the number of initial and maintenance doses needed to approach within a predetermined constant percent of the asymptotic minimum drug level in a given compartment. Since there is unlikely to be any general agreement as to the magnitude of this fixed percent, an arbitrary choice of ±1% of the asymptotic minimum value was selected for the purpose of illustration. Other fixed percentages of the asymptotic value, say ±5 and ±10%, would result in nomograms similar to the ones generated here and, therefore, will not be discussed.

THEORETICAL

Consider the case where the initial and maintenance doses of a drug are directly introduced into a given compartment from which the drug disappears in an apparent monoexponential manner by all processes. The number of doses necessary to approach within ±1% of the asymptotic minimum drug level can be estimated from Eq. 1, which was derived previously (10)

$$n \geqslant \left(\frac{t_{0.5}}{\tau}\right)\left(\frac{1}{\ln 2}\right) \ln Q \qquad \text{(Eq. 1)}$$

where n is the number of doses including the first one at zero time, $t_{0.5}$ is the apparent half-life for drug disappearance from the compartment, τ is the dosing interval in the same time units as for the half-life, and Q is defined by Eqs. 2–7. Let

$$B_i = B_m + B'' \qquad \text{(Eq. 2)}$$

where B_i is the initial dose, B_m is the constant maintenance dose, and B'' is the amount of drug in the compartment administered along with B_m as a part of the initial dose, and $B_i \geqslant B_m$.

Let

$$\beta = \frac{B''}{B^{\infty}_{\text{min.}}} = \frac{B''/V}{B^{\infty}_{\text{min.}}/V} \qquad \text{(Eq. 3)}$$

where β is the ratio of amounts or concentrations of drug, $B^{\infty}_{\text{min.}}$ is the asymptotic minimum amount of drug in the compartment one τ after a very large (or infinite) number of maintenance doses has been administered, and V is the constant for compartment volume (or apparent distribution volume for the compartment).

Let

$$\alpha_n = \frac{B^{(n)}_{\text{min.}}}{B^{\infty}_{\text{min.}}} = \frac{B^{(n)}_{\text{min.}}/V}{B^{\infty}_{\text{min.}}/V} \qquad \text{(Eq. 4)}$$

where α_n is the ratio of amounts or concentrations of drug compatible with integer values for n, $B^{(n)}_{\text{min.}}$ is the minimum amount of drug in the compartment one τ after the administration of the nth dose, and $B^{\infty}_{\text{min.}}$ and V have the same meaning as before. In this paper the value of $B^{(n)}_{\text{min.}}$ or $[B^{(n)}_{\text{min.}}/V]$ was arbitrarily set within ±1%

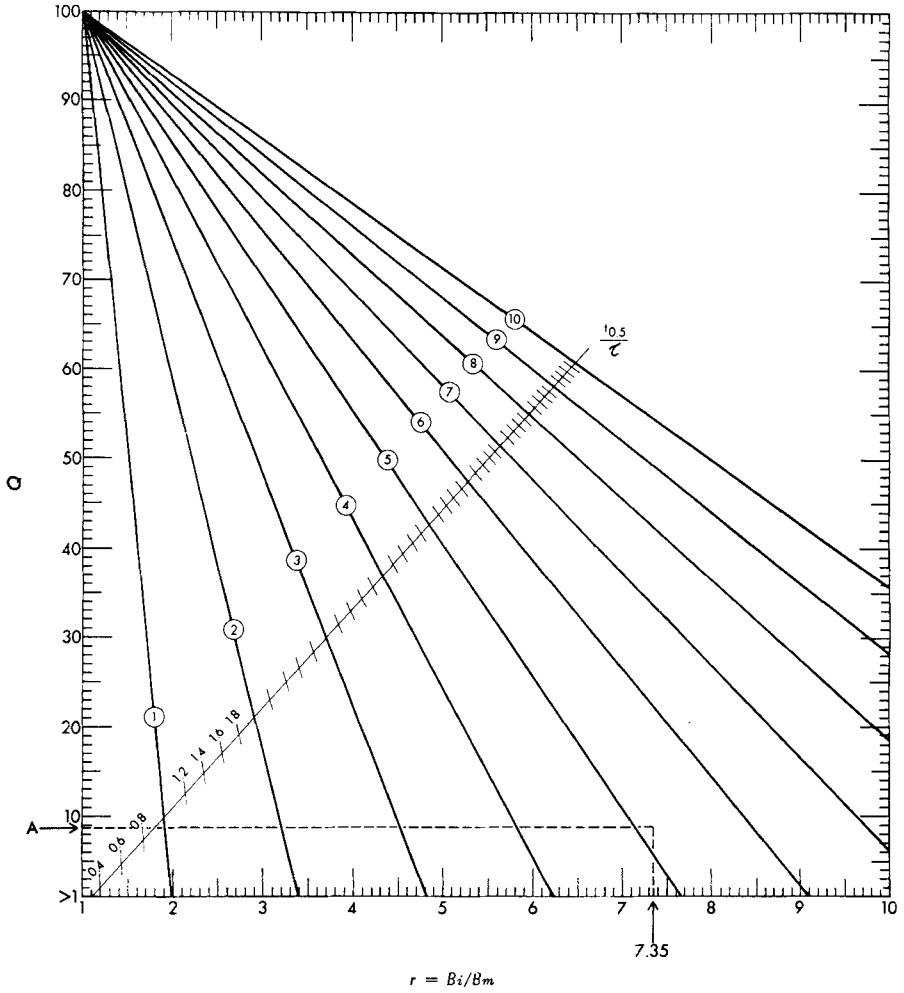

Figure 1—*Nomogram shows the relationship between* r *and* Q *for various* $t_{0.5}/\tau$ *values where* $\alpha = 0.99$. *Example for Animal A shows that* Q = 8.83 *when* r = 7.35 *and* $t_{0.5}/\tau = 5.18$.

of $B^{\infty}_{\text{min.}}$ or $(B^{\infty}_{\text{min.}}/V)$, so that it might not be possible to find values for α_n resulting in integer values for n. For α arbitrarily close to 1, say $|\alpha - 1| = 0.01$, it is desired to find the smallest n such that (10)

$$|\alpha_n - 1| = |e^{-n(\tau/t_{0.5})\ln 2}(\beta - 1)| \leqslant |\alpha - 1| \quad \text{(Eq. 5)}$$

Solving Eq. 5 for n yields

$$n \geqslant \left(\frac{t_{0.5}}{\tau}\right)\left(\frac{1}{\ln 2}\right)\ln\left(\frac{\beta - 1}{\alpha - 1}\right) \quad \text{(Eq. 6)}$$

Let

$$Q = \left(\frac{\beta - 1}{\alpha - 1}\right) = \left(\frac{1 - \beta}{1 - \alpha}\right) \quad \text{(Eq. 7)}$$

Substitution of Eq. 7 into Eq. 6 yields Eq. 1.

In this model, there is only one ratio, R, of the initial to the maintenance dose for a particular $t_{0.5}/\tau$ that results in constant values for $B^{\infty}_{\text{min.}}$ one τ after the first and all succeeding doses up to and including the nth dose. This ratio (11) is

$$R = \frac{B_i}{B_m} = \left[\frac{1}{1 - e^{-(\tau/t_{0.5})\ln 2}}\right] \quad \text{(Eq. 8)}$$

For purposes of convenience, let $X = (\tau/t_{0.5})\ln 2$.

There are many other possible values for the ratio B_i/B_m. Let

$$r = \frac{B_i}{B_m}, \qquad \text{where } r \neq R \quad \text{(Eq. 9)}$$

Substitution of Eq. 2 into Eq. 3 yields

$$\beta = \frac{B_i - B_m}{B^{\infty}_{\text{min.}}} = \frac{[(B_i - B_m)/V]}{(B^{\infty}_{\text{min.}}/V)} \quad \text{(Eq. 10)}$$

Substitution of Eq. 9 into Eq. 10 yields

$$\beta = \frac{(rB_m - B_m)}{B^{\infty}_{\text{min.}}} = \frac{(rB_m - B_m)/V}{B^{\infty}_{\text{min.}}/V} \quad \text{(Eq. 11)}$$

or

$$\beta = \frac{B_m(r - 1)}{B^{\infty}_{\text{min.}}} = \frac{B_m(r - 1)/V}{B^{\infty}_{\text{min.}}/V} \quad \text{(Eq. 12)}$$

It has been shown previously (11) that

$$B^{\infty}_{\text{min.}} = B_m\left(\frac{e^{-X}}{1 - e^{-X}}\right) \quad \text{(Eq. 13)}$$

Substitution of Eq. 8 into Eq. 13 yields

$$B^{\infty}_{\text{min.}} = B_m R e^{-X} \quad \text{(Eq. 14)}$$

Substitution of Eq. 12 into Eq. 7 yields

$$Q = \left(\frac{1}{1 - \alpha}\right)\left[1 - \frac{B_m(r - 1)}{B^{\infty}_{\text{min.}}}\right] \quad \text{(Eq. 15)}$$

Substitution of Eq. 14 into Eq. 15 yields

$$Q = \left(\frac{1}{1 - \alpha}\right)\left[1 - \frac{B_m(r - 1)}{B_m R e^{-X}}\right] \quad \text{(Eq. 16)}$$

and

$$Q = \left(\frac{1}{1 - \alpha}\right)\left[1 - \frac{(r - 1)}{Re^{-X}}\right] \quad \text{(Eq. 17)}$$

or

$$Q = \left(\frac{1}{1 - \alpha}\right)\left(1 - \frac{r}{Re^{-X}} + \frac{1}{Re^{-X}}\right) \quad \text{(Eq. 18)}$$

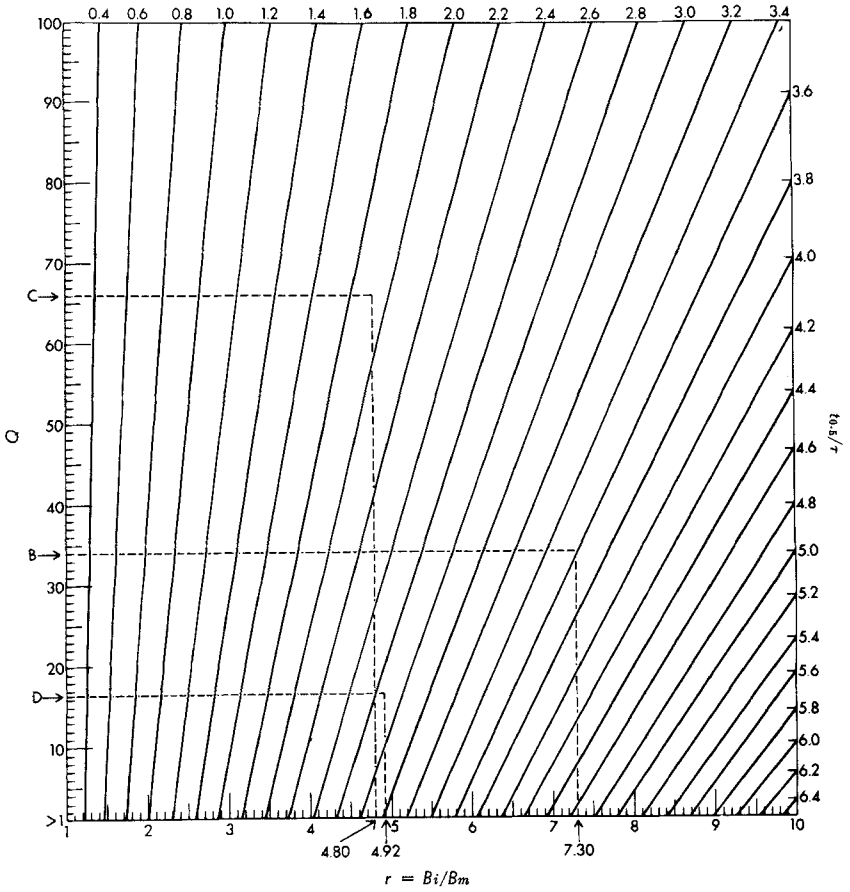

Figure 2—*Nomogram shows the relationship between* r *and* Q *for various* $t_{0.5}/\tau$ *values where* $\alpha = 1.01$. *Example for Animal B shows that* Q = 34.2 *when* r = 7.30 *and* $t_{0.5}/\tau = 3.60$. *Consult Table I for data on Animals C and D.*

Rearranging Eq. 18 gives

$$Q = \left(\frac{1}{1-\alpha}\right)\left(1 - \frac{re^{+X}}{R} + \frac{e^{+X}}{R}\right) \qquad \text{(Eq. 19)}$$

Substitution of Eq. 8 into the right-hand term of Eq. 19 gives

$$Q = \left(\frac{1}{1-\alpha}\right)\left[1 - \frac{re^{+X}}{R} + (e^{+X})(1 - e^{-X})\right] \qquad \text{(Eq. 20)}$$

and

$$Q = \left(\frac{1}{1-\alpha}\right)\left(e^{+X} - \frac{re^{+X}}{R}\right) \qquad \text{(Eq. 21)}$$

or

$$Q = e^{+X}\left(\frac{1 - \frac{r}{R}}{1-\alpha}\right) \qquad \text{(Eq. 22)}$$

Equation 22 can be rearranged into an equation for a straight line:

$$Q = \left[\frac{e^{+X}}{(1-\alpha)}\right] - \left[\frac{e^{+X}/R}{(1-\alpha)}\right] r \qquad \text{(Eq. 23)}$$

Thus, a plot of *r versus Q* would result in an intercept of

$$\left[\frac{e^{+(\tau/t_{0.5})\ln 2}}{1-\alpha}\right]$$

When *r* is 1, the value of *Q* will be +100 when α is 0.99, and it will be −100 when α is 1.01. The slope

$$\left[\frac{e^{+(\tau/t_{0.5})\ln 2/R}}{1-\alpha}\right]$$

will be negative when α is 0.99 and positive when α is 1.01.

The time, *t*, needed for amounts or concentrations to reach within ±1% of the corresponding asymptotic values one τ after the *n*th dose can be calculated from the relationship

$$t = n\tau \qquad \text{(Eq. 24)}$$

RESULTS AND DISCUSSION

Figures 1 and 2[1] show the plot of *r versus Q* where *r* ranges from 1 to 10. In Fig. 1 the value of $t_{0.5}/\tau$ varies from 0.4 to 10, and in Fig. 2 the value of $t_{0.5}/\tau$ varies from 0.4 to 6.4. The values for *Q* in both figures vary from >1 to 100. The reasons that *Q* must be greater than +1 at all times have been discussed elsewhere (10). Two examples, using literature data, will illustrate how Figs. 1–3 can be used to solve for the quantities *n* and *t*. The first example involves multiple subcutaneous drug administration and the second involves multiple oral drug administration.

Example 1: Multiple Subcutaneous Injections—Ballard and Menczel (10) administered dilute aqueous benzyl alcohol solutions directly onto the subcutaneous tissue of anesthetized rats and followed drug concentration changes as a function of time. The drug disappeared from the subcutaneous region compartment in an apparent monoexponential manner after each dose administration. A summary of the data obtained from Animals A through D (10, 11) is found in Table I. In Fig. 1 it can be seen for Animal A, when $r = 7.35$, $\alpha = 0.99$, and $t_{0.5}/\tau = 5.18$, that $Q \cong 8.83$. In Fig. 2 the same procedure used for Animal D is followed for Animals B and C to determine *Q* since they, too, have a value for $\alpha = 1.01$.

When using Figs. 1 and 2, it is not necessary in a particular case to know in advance whether $\alpha = 0.99$ or $\alpha = 1.01$. For example, in Fig. 1, only Animal A has the $t_{0.5}/\tau$ value needed to make an estimate of *Q* for its *r* value. Similarly, in Fig. 2, only Animals B, C, and D have the $t_{0.5}/\tau$ value needed to make an estimate of *Q* for their respective *r* values.

In Fig. 3 a plot of *n versus* $(t_{0.5}/\tau)$ is based upon Eq. 1. Once a given value for *Q* can be estimated from Fig. 1 or 2 using the appropriate values for *r* and $t_{0.5}/\tau$, it is possible to estimate *n* from

[1] Enlarged copies of Figs. 1, 2, and 3 are available upon request.

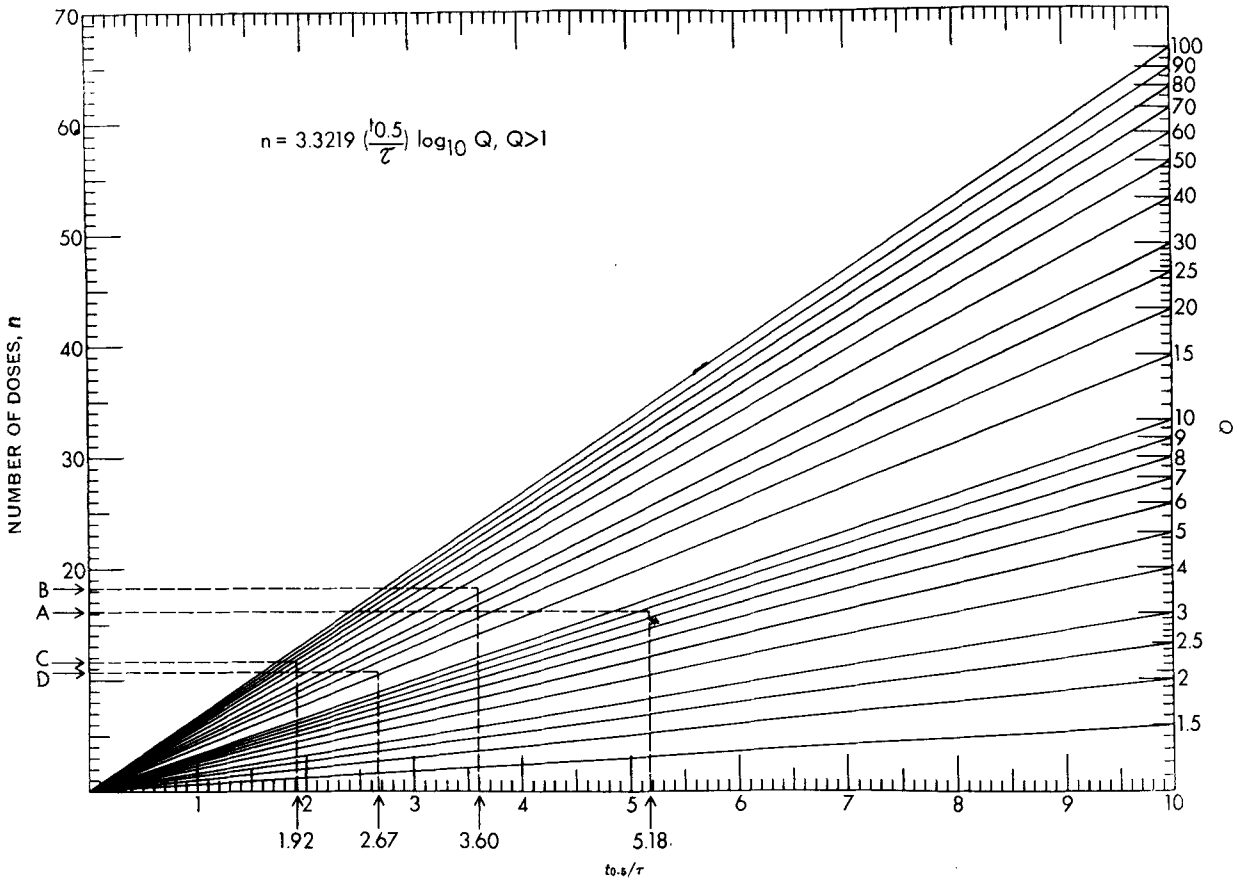

Figure 3—*Nomogram shows the relationship between* Q *and* n *for various values of* $t_{0.5}/\tau$. *Example for Animal A shows that when* Q = *8.83 and* $t_{0.5}/\tau$ = *5.18, then* n > *16. Consult Table I for data on Animals B, C, and D.*

Fig. 3 for the same values for Q and $t_{0.5}/\tau$. Obviously, it is also possible to proceed in the reverse direction; if a given value for n is desired, it should be possible to use Fig. 3 and the appropriate Fig. 1 or 2 to estimate the required B_i/B_m value for a fixed value[2] of $t_{0.5}/\tau$.

When apparent monoexponential loss of drug occurs from a compartment such as a subcutaneous absorption cell, the previous mathematical methods are correct. However, when the concentration *versus* time course of a drug in a given compartment is best described by some polyexponential function, the previous mathematical derivations must be used cautiously. Wagner *et al.* (8) discussed other phenomena which may invalidate the procedures discussed for multiple-dosing calculations.

Nevertheless, with carefully selected clinical data, it is possible, without introducing too much error, to use equations derived in this paper and the nomograms shown in Figs. 1–3 to estimate the number of doses and time needed to approach within ±1% of the asymptotic minimum drug level in the compartment. An example using these equations on data obtained from a sulfonamide having a short absorption half-life and long biological half-life in humans will illustrate the method of calculating n from a knowledge of the two ratios: $t_{0.5}/\tau$ and B_i/B_m.

Example 2: Multiple Oral Dosing—Krüger-Thiemer *et al.* (12) administered sulfamethoxypyrazine orally to three healthy test subjects using two different dosing regimens. In the first experiment, the subjects received an initial dose of 400 mg. of the drug followed by six[3] 100-mg. maintenance doses at a dosing interval of 24 hr. The plasma concentration of the drug was followed for 216 hr. In the second experiment, the same subjects received an initial dose of 2000 mg. followed by three 1500-mg. maintenance doses at a dosing interval of 168 hr. The plasma concentration of the drug was followed for 624 hr. in one subject and for 672 hr. in the other two subjects. The authors assumed that a single body compartment provided a sufficient description of drug distribution which took into account drug binding to plasma proteins. In this model, two first-order rate constants were considered to describe drug absorption from the gastrointestinal tract and drug elimination mainly by metabolism and renal excretion. Since the absorption half-life of the drug from the gastrointestinal tract was short (0.4–0.7 hr.) compared to the elimination half-life (50–69 hr.), only a small error is made if one assumes that the drug was being administered by a rapid intravenous injection instead of by oral administration. If it is valid to assume that the absorption step is nearly instantaneously rapid, then it should be possible to use the pharmacokinetic data summarized in the top half of Table II for the three subjects to estimate the number of doses, n, required to approach

Table I—Data and Derived Constants from Subcutaneous Multiple-Dosing Experiments with Benzyl Alcohol Required for Substitution into Figs. 1–3 to Estimate the Total Number of Doses Needed to Approach within ±1% of $B^{\infty}_{min.}$ (10, 11)

Constant	Animal A	Animal B	Animal C	Animal D
$t_{0.5}/\tau$[a]	5.18	3.60	1.92	2.67
α[b]	0.99	1.01	1.01	1.01
r[c]	7.35	7.30	4.80	4.92
R[d]	7.97	5.70	3.29	4.37
Q[e]	8.83	34.2	65.9	16.4
n[f]	>16	>18	>11	>10

[a] This ratio is defined in Eq. 1. [b] This term was arbitrarily set at 0.99 or 1.01 so that $B^{n}_{min.}$ would approach within ±1% of $B^{\infty}_{min.}$. [c] Defined by Eq. 9. [d] Defined by Eq. 8. [e] Defined by Eq. 7. [f] Defined by Eq. 1.

[2] The model 9100 Hewlett-Packard calculator (Palo Alto, Calif.) was programmed to solve the equations needed to construct Figs. 1–3 and to calculate the values contained in Tables I and II.

[3] In the work by Krüger-Thiemer *et al.* (12), Fig. 5 shows that six 100-mg. maintenance doses were administered to the three subjects. Tables VIII and XII were in error (13) because they indicated that only four 100-mg. maintenance doses were administered.

Table II—Data and Derived Constants from Oral Multiple-Dosing Experiments with Sulfamethoxypyrazine Required for Substitution into Figs. 1–3 to Estimate the Total Number of Doses and Time Needed to Approach within ±1% of $B^{\infty}_{min.}$ (12, 14)

Constant	Subject: Be.[i] Expt. 1	Be.[i] Expt. 2	Ste.[i] Expt. 1	Ste.[i] Expt. 2	Su.[i] Expt. 1	Su.[i] Expt. 2
$t_{0.5}$ (hr.)[a]	61.5	69.2	58.7	64.6	50.4	51.1
τ (hr.)[b]	24	168	24	168	24	168
$t_{0.5}/\tau$	2.56	0.41	2.45	0.39	2.10	0.30
B_i[c]	400 mg.	2000 mg.	400 mg.	2000 mg.	400 mg.	2000 mg.
B_m[d]	100 mg.	1500 mg.	100 mg.	1500 mg.	100 mg.	1500 mg.
r[e]	4	1.33	4	1.33	4	1.33
R[f]	4.22	1.23	4.05	1.20	3.56	1.11
Q[g]	6.81	45.87	1.71	68.68	17.32	191.89
n[h]	>7	>2	>1	>2	>8	>2
	(7.09)	(2.27)	(1.89)	(2.35)	(8.64)	(2.31)
t (days)[i]	7	14	1	14	8	14

Constant	Age Groups: Newborns	Infants	Children	Adults	Aged
$t_{0.5}$ (hr.)[a]	135.6	53.9	51.0	63.3	98.2
τ (hr.)[b]	24	24	24	24	24
$t_{0.5}/\tau$	5.65	2.25	2.13	2.64	4.09
B_i[c]	12 mg./kg.	8.2 mg./kg.	12 mg./kg.	750 mg.	600 mg.
B_m[d]	1.34 mg./kg.	1.9 mg./kg.	3 mg./kg.	150 mg.	100 mg.
r[e]	8.96	4.32	4.0	5.0	6.0
R[f]	8.66	3.77	3.59	4.33	6.42
Q[g]	3.83	19.89	15.70	20.23	7.70
n[h]	>10	>9	>8	>11	>12
	(10.96)	(9.69)	(8.44)	(11.44)	(12.05)
t (days)[i]	10	9	8	11	12

[a] Defined by Eq. 1. [b] Dosing time interval. [c] Initial dose. [d] Maintenance dose. [e] Defined by Eq. 9. [f] Defined by Eq. 8. [g] Defined by Eq. 7. [h] Defined by Eq. 1. [i] Defined by Eq. 24. [j] Abbreviations for the subjects used in *Reference 12.*

within ±1% of the asymptotic minimum drug level and the time, t, needed to reach this level for the two dosing regimens.

In Table II, it can be seen that under conditions defined in Experiment 1 for the three subjects, 1–8 days are required to approach within ±1% per cent of the asymptotic minimum drug level in the body expected one τ after a large (or infinite) number of maintenance doses has been administered. On the other hand, under conditions defined in Experiment 2 for the three subjects, the time needed to approach within ±1% of the asymptotic minimum drug level is 14 days. Thus, if it is therapeutically desirable to approach within ±1% of the asymptotic minimum drug level rapidly, the dosage regimen defined by the conditions of Experiment 1 would be preferred over that defined by the conditions of Experiment 2.

Sereni *et al.* (14) used the Krüger-Thiemer methods to study the pharmacokinetics of orally administered sulfamethoxypyrazine, using subjects of five different age groups. The subjects were newborns (2–3 days), infants (1–12 months), children (4–9 years), adults, and the aged (>70 years). The bottom half of Table II summarizes some of the data and other derived constants for the various age groups from the paper by Sereni *et al.* (14). It can be seen from Table II that from 8–12 days are needed to reach within ±1% of the asymptotic minimum drug level expected one τ after a large (or infinite) number of doses has been administered to these five different age groups.

In this example, the basic assumption is that the apparent biological half-life of the drug remains substantially the same after one or many doses has been administered. The data presented by Krüger-Thiemer *et al.* (12) seem to support this assumption for sulfamethoxypyrazine. However, with other drugs the apparent biological half-life may change, depending upon the number of maintenance doses administered. For example, when 500 mg. of tetracycline as the phosphate complex was administered orally to 10 test subjects every 12 hr., the apparent biological half-life increased from 6.3 hr. for the 1st day to 10.0 hr. for the 5th to 6th days (15). It is not yet clear why the apparent biological half-life of tetracycline as the phosphate complex administered orally to humans seems to change depending upon the number of doses administered. The equations derived in this paper cannot be used in cases where the apparent half-life of the drug in a given compartment varies during the dosing regimen.

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