ACKNOWLEDGMENTS AND ADDRESSES

Received January 28, 1974, from the *Toxicology Department, Corporate Research, and Pharmacy Research Department, Consumer Products Division, Miles Laboratories, Inc., Elkhart, IN 46514.*

Accepted for publication March 1, 1976.

The authors thank C. E. Myers and L. J. Baker for their expert technical assistance and J. L. Allen and T. Janakiraman for statistical analysis of the data.

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Quick Estimation of Kinetic Parameters for a Compartment with Exponential Absorption Rate and First-Order Elimination Rate

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Abstract ◻ Two methods are presented for the quick estimation of kinetic parameters for a compartment with an exponential absorption rate and a first-order elimination rate. The first method is by direct computation from the observed levels of substance in the compartment at times t, $2t$, and $3t$, where t is arbitrary. The second method uses a numerical table to estimate the parameters from the observed peak level, the time of the peak level (or the time when the level rises to half of the peak level), and the time when the level has declined to half of its peak value. Some approximation equations also are given.

Keyphrases ◻ Kinetic parameters—compartment with exponential absorption rate and first-order elimination rate, two methods for quick estimation ◻ Pharmacokinetics—compartment with exponential absorption rate and first-order elimination rate, two methods for quick estimation of kinetic parameters

If the rate of absorption of a substance into an initially empty, well-stirred compartment declines exponentially with time and the rate of elimination is first order, then the quantity or concentration, y, of the substance in the compartment is a function of time, t, of the general form:

$$y = \frac{C(e^{-k_1 t} - e^{-k_2 t})}{k_2 - k_1} \qquad \text{(Eq. 1)}$$

where C, k_1, and k_2 are constants. The method usually recommended for estimating these constants from experimental data is a graphical procedure known as "peeling," "feathering," or the "method of residuals" (1, pp. 281–292), complemented by least-squares adjustment by computer (1, 2). The graphical procedure can be computerized, and these methods are entirely satisfactory if suitable computer programs and services are available. Without a computer, however, these methods are time consuming and are quite unwieldy for preliminary evaluation of data, rough comparison of published reports, and double-checking calculations.

This report describes methods of rapid, direct computation of C, k_1, and k_2 from experimental data; these methods may be useful for applications not requiring high accuracy or careful statistical weighting.

THEORY AND DISCUSSION

Estimation from y Values at t, $2t$, and $3t$—In principle, any three data points will determine the three parameters. In practice, however, the resulting three simultaneous equations cannot always be solved for the parameters. Therefore, direct computation of the parameters requires a suitable selection of data points.

Let t be any convenient time and let y_1, y_2, and y_3 be the observed levels at t, $2t$, and $3t$, respectively. Equation 1 gives:

$$y_j = \frac{C(e^{-k_1 jt} - e^{-k_2 jt})}{k_2 - k_1} \qquad \text{(Eq. 2)}$$

where j = 1, 2, or 3. For the solution of these three simultaneous equations, let:

$$r = +\sqrt{\frac{y_1 y_3}{y_2^2} - \frac{3}{4}} \qquad \text{(Eq. 3)}$$

Then:

$$k_1 = -\frac{1}{t}\log_e\left[\frac{y_2}{y_1}\left(\frac{1}{2} + r\right)\right] \qquad \text{(Eq. 4)}$$

$$k_2 = -\frac{1}{t}\log_e\left[\frac{y_2}{y_1}\left(\frac{1}{2} - r\right)\right] \qquad \text{(Eq. 5)}$$

and:

$$C = \frac{y_1^2(k_2 - k_1)}{2y_2 r} \qquad \text{(Eq. 6)}$$

The labeling of the constants k_1 and k_2 is entirely arbitrary. The conventions adopted here regarding the algebraic sign of r (Eqs. 3–5) assign the label k_2 to the larger of the two. If $r = 0$, then $k_1 = k_2 = k$ and Eq. 1 takes the limiting form:

$$y = Cte^{-kt} \qquad \text{(Eq. 7)}$$

If the quantity under the radical in Eq. 3 is negative, the data are inconsistent with the model underlying Eq. 1.

Equations 3–6 become simpler if t is selected on the rising limb of the y curve (Fig. 1) in such a way that $2t$ intercepts the falling limb at just the same level; *i.e.*, $y_2 = y_1$. Then the limiting case ($k_1 = k_2 = k$, Eq. 7) will have $y_3 = (3/4)y_1$ (*cf.*, Eq. 3).

The use of Eqs. 3–6 may be illustrated by the example of Fig. 1. The steps for estimating the parameters are:

1. From the curve of Fig. 1, read the values of y at t = 2, 4, and 6: y_1 = 1.85, y_2 = 1.43, and y_3 = 1.02, respectively.
2. Compute $r = \sqrt{(1.85)(1.02)/(1.43)^2 - 0.75} = 0.416$ and $y_2/y_1 = 1.43/1.85 = 0.773$.
3. Compute $k_1 = -(1/2)\log_e[0.773(0.5 + 0.416)] = 0.17$, $k_2 = -(1/2)\log_e[0.773(0.5 - 0.416)] = 1.4$, and $C = fDk_a/V = (1.85)(1.4 - 0.17)/[2(0.773)(0.416)] = 3.5$.

Like any method of fitting the curve of Fig. 1, this analysis does not tell which of the two constants, k_1 (the smaller) or k_2 (the larger), is identified with k_a or k_e, nor does it evaluate the several factors of the coefficient C.

Estimation from Peak Level, y_m, Time of Peak Level, t_m, and Time of Decline to Half of Peak Level, t_{h_2}—Let y_m be the peak level, t_m be the time of the peak level, t_{h_1} be the time when the rising level first reaches $y_m/2$, and t_{h_2} be the time (after t_m) when the declining level reaches $y_m/2$ (Fig. 1). The theoretical equations (Eq. 1) for these ob-

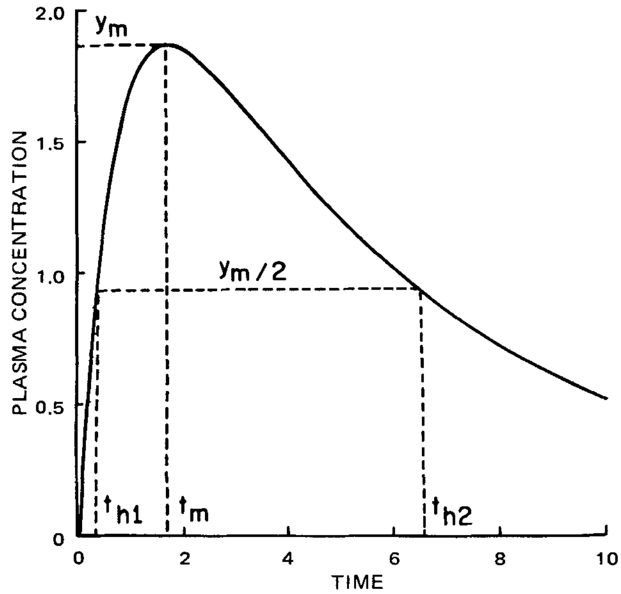

Figure 1—*Plasma concentration–time profile for a one-compartment system with absorption rate constant* $k_a = 1.4$, *elimination rate constant* $k_e = 0.17$, *volume of distribution* $V = 40$, *dose* $D = 100$, *and fraction absorbed* $f = 1$. *The plasma concentration* y *obeys the equation* $y = (fDk_a/V)[exp(-k_et) - exp(-k_at)]/(k_a - k_e)$, *where* t *is time* (cf., *Ref.* 2, *p.* 292). *The dashed lines indicate the peak level* y_m, *the time of the peak level* t_m, *the time* t_{h_1} *when the rising level first reaches* $y_m/2$, *and the time* t_{h_2} *when the declining level reaches* $y_m/2$.

servable values cannot be solved for the constants C, k_1, and k_2, so a numerical table is used (Table I). This table is based on the fact that if the value of the ratio t_{h_2}/t_m is known, the normalized parameters k_1/t_m, k_2/t_m, and Ct_m/y_m are entirely determined; from these values and the observed y_m and t_m, the constants k_1, k_2, and C are easily computed. The table also includes the ratio t_{h_2}/t_{h_1} in case the available value of t_m is more uncertain than that of t_{h_1}.

Computations for Table I were done as follows. Let $\kappa = k_2/k_1$. As before,

Table I—Normalized Parameters for a Compartment with Exponential Absorption and First-Order Elimination[a]

t_{h_2}/t_m	k_1t_m	k_2t_m	Ct_m/y_m	t_{h_2}/t_{h_1}
2.68[b]	1.000	1.00	2.72[c]	11.5[d]
2.70	0.840	1.18	2.73	11.7
2.75	0.726	1.34	2.76	12.0
2.80	0.657	1.45	2.79	12.3
2.85	0.607	1.53	2.82	12.6
2.90	0.567	1.61	2.84	12.9
2.95	0.534	1.68	2.87	13.3
3.00	0.505	1.74	2.89	13.6
3.10	0.459	1.86	2.94	14.2
3.20	0.422	1.95	2.98	14.8
3.30	0.392	2.04	3.02	15.5
3.40	0.367	2.12	3.06	16.1
3.50	0.345	2.20	3.10	16.7
3.60	0.326	2.26	3.14	17.4
3.70	0.309	2.33	3.17	18.0
3.80	0.294	2.39	3.20	18.7
3.90	0.281	2.44	3.24	19.3
4.00	0.269	2.50	3.27	20.0
4.10	0.258	2.55	3.30	20.6
4.20	0.248	2.60	3.33	21.3
4.30	0.239	2.64	3.36	22.0
4.40	0.230	2.69	3.38	22.6
4.50	0.222	2.73	3.41	23.3
4.60	0.215	2.77	3.44	24.0
4.70	0.208	2.81	3.46	24.7
4.80	0.202	2.85	3.49	25.3
4.90	0.196	2.89	3.51	26.0
5.00	0.190	2.92	3.53	26.7
5.20	0.180	2.99	3.58	28.1
5.40	0.171	3.06	3.62	29.5

Table I—(*Continued*)

t_{h_2}/t_m	k_1t_m	k_2t_m	Ct_m/y_m	t_{h_2}/t_{h_1}
5.60	0.162	3.12	3.67	30.9
5.80	0.155	3.18	3.71	32.3
6.00	0.148	3.23	3.75	33.7
6.20	0.142	3.28	3.78	35.1
6.40	0.136	3.34	3.82	36.6
6.60	0.131	3.38	3.86	38.0
6.80	0.126	3.43	3.89	39.5
7.00	0.121	3.48	3.92	41.0
7.20	0.117	3.52	3.96	42.4
7.40	0.113	3.56	3.99	43.9
7.60	0.110	3.60	4.02	45.4
7.80	0.106	3.64	4.05	46.9
8.00	0.103	3.68	4.08	48.4
8.20	0.100	3.71	4.11	50.0
8.40	0.0972	3.75	4.13	51.5
8.60	0.0945	3.78	4.16	53.0
8.80	0.0920	3.82	4.19	54.6
9.00	0.0896	3.85	4.21	56.1
9.20	0.0873	3.88	4.24	57.7
9.40	0.0851	3.91	4.26	59.2
9.60	0.0831	3.94	4.28	60.8
9.80	0.0811	3.97	4.31	62.4
10.00	0.0792	4.00	4.33	64.0
10.5	0.0749	4.07	4.39	67.9
11.0	0.0710	4.13	4.44	72.0
11.5	0.0676	4.20	4.49	76.0
12.0	0.0644	4.26	4.54	80.1
12.5	0.0615	4.31	4.58	84.2
13.0	0.0589	4.36	4.63	88.4
13.5	0.0565	4.42	4.67	92.6
14.0	0.0543	4.46	4.71	96.8
14.5	0.0522	4.51	4.75	101
15.0	0.0503	4.56	4.79	105
15.5	0.0485	4.60	4.83	110
16.0	0.0469	4.64	4.86	114
16.5	0.0453	4.68	4.90	118
17.0	0.0439	4.72	4.93	123
17.5	0.0426	4.76	4.97	127
18.0	0.0413	4.80	5.00	132
18.5	0.0401	4.83	5.03	136
19.0	0.0390	4.87	5.06	140
19.5	0.0379	4.90	5.09	145
20.0	0.0369	4.93	5.12	149
21.0	0.0350	5.00	5.17	159
22.0	0.0333	5.06	5.23	168
23.0	0.0318	5.11	5.28	177
24.0	0.0304	5.17	5.33	186
25.0	0.0291	5.22	5.37	196

[a] For values of t_{h_2}/t_m larger than those shown here, the following equations give estimates accurate to within 5%:

$$k_1 \simeq \frac{(\log_e 2)}{t_{h_2} - t_m} \quad k_2 \simeq \frac{(\log_e 2)}{t_{h_1}} \quad C \simeq k_2 y_m$$

If t_{h_1} is not available, k_2t_m can be estimated from the recursion equation $k_{2(i+1)}t_m = k_1t_m - \log_e(k_1t_m) + \log_e(k_{2i}t_m)$, where $k_{2i}t_m$ and $k_{2(i+1)}t_m$ are the ith and $(i+1)$th successive approximations to k_2t_m, and a suitable starting estimate, $k_{21}t_m$, is $k_1t_m - \log_e(k_1t_m)$ or just $-\log_e(k_1t_m)$. [b] The value is 2.67835. A value of t_{h_2}/t_m smaller than this is inconsistent with the model on which Eq. 1 is based. [c] 2.71828 = e. [d] The value is 11.54466.

the convention is adopted that $k_2 \geq k_1$ and, therefore, $\kappa \geq 1$. When $t = t_m$, $dy/dt = 0$ and Eqs. 1 and 7 give:

$$k_1t_m = \frac{\log_e \kappa}{\kappa - 1} \quad (k_1 \neq k_2) \qquad \text{(Eq. 8a)}$$

$$k_1t_m = 1 \quad (k_1 = k_2) \qquad \text{(Eq. 8b)}$$

and:

$$k_2t_m = \kappa k_1 t_m \qquad \text{(Eq. 9)}$$

Equations 8*a*, 8*b*, and 9 are used to substitute for k_1 and k_2 in Eqs. 1 and 7 to obtain:

$$\frac{y}{y_m} = \frac{\kappa^{-(t/t_m)/(\kappa-1)} - \kappa^{-[\kappa(t/t_m)]/(\kappa-1)}}{\kappa^{-1/(\kappa-1)} - \kappa^{-\kappa/(\kappa-1)}} \qquad \text{(Eq. 10a)}$$

$$\frac{y}{y_m} = \frac{\kappa^{-[(t/t_m)-1]/(\kappa-1)}\,(\kappa^{(t/t_m)} - 1)}{\kappa - 1} \qquad (\kappa \neq 1) \qquad \text{(Eq. 10}b\text{)}$$

$$\frac{y}{y_m} = (t/t_m)e^{-[(t/t_m)-1]} \qquad (\kappa = 1) \qquad \text{(Eq. 10}c\text{)}$$

Let $\theta_1 = t_{h_1}/t_m$ and $\theta_2 = t_{h_2}/t_m$; then, from Eqs. 10*b* and 10*c*:

$$\frac{1}{2} = \frac{\kappa^{-[\kappa(\theta-1)]/(\kappa-1)}(\kappa^{\theta} - 1)}{\kappa - 1} \qquad (\kappa \neq 1) \qquad \text{(Eq. 11}a\text{)}$$

$$\frac{1}{2} = \theta e^{-(\theta-1)} \qquad (\kappa = 1) \qquad \text{(Eq. 11}b\text{)}$$

for $\theta = \theta_1$ or θ_2. An iterative method [a one-dimensional modified version of the flexible simplex method described by Himmelblau (3)] was used to compute θ for a given κ or κ for a given θ from Eqs. 11*a* and 11*b*. (For a given κ, the algorithm employed converged either to θ_1 or θ_2, depending on the initial estimate.) For large κ and θ values, the computation of the right-hand side of Eqs. 11*a* and 11*b* produced intermediate values too large for the computer. To avoid these overflows, an alternative equation was used when κ was greater than 50 and θ was greater than 9:

$$\frac{1}{2} = \frac{\kappa^{(\kappa-\theta)/(\kappa-1)}}{\kappa - 1} \qquad \text{(Eq. 12)}$$

This equation is derived from Eqs. 11*a* and 11*b* by replacing the term $\kappa^{\theta} - 1$ by κ^{θ} and multiplying out the numerator.

Finally, Eqs. 8*a*, 8*b*, and 9 are used to substitute for k_1 and k_2 in Eqs. 1 and 7 to obtain:

$$\frac{Ct_m}{y_m} = \frac{\kappa^{\kappa/(\kappa-1)}\log_e \kappa}{\kappa - 1} \qquad (\kappa \neq 1) \qquad \text{(Eq. 13}a\text{)}$$

$$\frac{Ct_m}{y_m} = e \qquad (\kappa = 1) \qquad \text{(Eq. 13}b\text{)}$$

The use of Table I may be illustrated by the example of Fig. 1. The steps in estimating the parameters are:

1. From the curve of Fig. 1, read $t_m = 1.7$ and $y_m = 1.88$.
2. Compute $y_m/2 = 0.94$.
3. From the curve of Fig. 1, read $t_{h_2} = 6.5$ (where $y = 0.94$).
4. Compute $t_{h_2}/t_m = 3.8$.
5. From Table I, read $k_1t_m = 0.294$, $k_2t_m = 2.39$, and $Ct_m/y_m = 3.20$.
6. Compute $k_1 = 0.294/1.7 = 0.17$, $k_2 = 2.39/1.7 = 1.4$, and $C = fDk_a/V = (3.20)(1.88)/1.7 = 3.5$.

If t_{h_1} can be determined more accurately than t_m, the first four steps can be modified as follows:

1. From the curve of Fig. 1, read $y_m = 1.88$.
2. Compute $y_m/2 = 0.94$.
3. From the curve of Fig. 1, read $t_{h_1} = 0.35$ and $t_{h_2} = 6.5$.
4. Compute $t_{h_2}/t_{h_1} = 18.6$.

Since this value of t_{h_2}/t_{h_1} lies between the tabulated values, interpolation might be done. For most purposes, however, it is sufficiently accurate to take the normalized parameter values corresponding to the closest tabulated value of t_{h_2}/t_{h_1}, *i.e.*, 18.7.

The accuracy of this method is obviously limited by the accuracy of determination of t_m and t_{h_2} or t_{h_1}. These parameters, especially t_m and t_{h_1}, are likely to be quite inaccurately known when only a small number of data points are available, as is commonly the case. The values of k_1 and k_2 are especially uncertain when the ratio t_{h_2}/t_m is less than 3 or 3.5, because in this region the dependence of k_1t_m and k_2t_m on t_{h_2}/t_m is quite steep (Table I). These limitations on accuracy must be kept in mind when this method is used.

Approximation Equations—Attempts to find simple approximation equations for k_1, k_2, and C in terms of t_m, t_{h_1}, t_{h_2}, and y_m yielded only two that were both simple and reasonably accurate:

$$C = (\log_e 2)y_m/t_{h_1} = 0.693y_m/t_{h_1} \qquad \text{(Eq. 14)}$$

and:

$$k_1 = (\log_e 2)/(t_{h_2} - 1.5t_m) = 0.693/(t_{h_2} - 1.5t_m) \qquad \text{(Eq. 15)}$$

Equation 14 gives slightly high values, accurate to within 5% if $t_{h_2}/t_m > 4.7$ and to within 10% otherwise. Equation 15 gives values within ±5% if $t_{h_2}/t_m > 3.15$ and within 10% if $t_{h_2}/t_m > 2.95$; but for lower values of t_{h_2}/t_m, it gives values of k_1 that are as much as 41% too low.

Equation 15 may be convenient for estimating the elimination rate constant from plasma level–time curves following oral administration, assuming the elimination rate constant is smaller than the absorption rate constant. It is essentially the familiar equation for intravenous administration, $k_1 = (\log_e 2)/t_{h_2}$, corrected for gradual absorption by the term $-1.5t_m$.

The parameter k_2 can be estimated from k_1 and t_m by the recursion equation given in footnote *a* to Table I. Several iterations may be necessary if $k_1t_m > 0.1$, and a programmable calculator is convenient for doing these calculations.

CONCLUSIONS

The described methods appear to be the best solutions to the problem of getting rough estimates of the parameters of Eq. 1 with minimum computation. These methods do not verify that the data in question do in fact obey Eq. 1; therefore, these methods could be misleading if applied to data that do not obey Eq. 1. If such misapplications are avoided, however, these methods may prove useful, especially for preliminary evaluation of data, rough comparison of published reports, and double-checking calculations.

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ACKNOWLEDGMENTS AND ADDRESSES

Received January 12, 1976, from the *Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH 03755.*

Accepted for publication March 8, 1976.