$$\frac{k_{-1}}{(k_1 + k_{-1})} = \frac{100 - \%\Pi_{eq}}{100} \quad \text{(Eq. A5)}$$

$$k_{-1} = \frac{100 - \%\Pi_{eq}}{100}(k_1 + k_{-1}) \quad \text{(Eq. A6)}$$

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Multiple-Dose Kinetics of Oral Anticoagulants: Methods of Analysis and Optimized Dosing

THEOFANIS G. THEOFANOUS▲ and RONALD G. BARILE

Abstract □ A mathematical technique for estimating the kinetic parameters that control patient response to oral anticoagulant administration is presented. The technique utilizes routinely obtained and recorded data such as anticoagulant dose regimen and prothrombin times. It is possible to apply during any stage of therapy and to gain predictive capability from data covering the measured response over a minimum period of 2 days. The applicability of the technique is demonstrated by direct comparison with two actual patient records.

Keyphrases □ Anticoagulant therapy—estimation of kinetic response parameters using routine clinical data, equations, compared to patient records □ Multiple-dosing kinetics, oral anticoagulants—estimation of response parameters using routine clinical data, equations, compared to patient records □ Prothrombin time data—used to estimate kinetic response parameters to oral anticoagulant therapy, equations □ Dosing regimens, oral anticoagulants—determined using estimated kinetic response parameters based on routine clinical data, equations

The pharmacological effects of hypoprothrombinemic anticoagulant drugs vary widely among individuals and preclude a universal response to a fixed dose of these agents. A given dosage schedule may be totally inadequate to prevent thrombosis in one individual but may cause hemorrhage in another (1). This fact, as well as a need sometimes to readjust therapeutic levels of activity *during* therapy (1), obviously necessitates patient individualization of dosing regimens for these drugs and clearly emphasizes the need for predictive relationships between dosage regimens and the magnitude of drug response they produce.

The first and basic steps toward such an individualization are the elucidation of the basic biochemical mechanisms involved in the synthesis of prothrombin complex activity and an assessment of the relevant intrinsic kinetics. The excellent works of other researchers (2–9) cover the whole range of development of this stage, from the pioneering level up to a complete and extensive verification of the proposed kinetic model.

Following these fundamental works, the "engineering aspects" of the process remain to be developed in detail to close the gap between laboratory (controlled) studies and health care applications and thus to arrive at a reliable and convenient aid which could be used by the doctor in prescribing anticoagulant dose regimens. This study reports the results from the authors' initial efforts in this direction. In particular, the following may be recognized as two major engineering aspects:

1. *Parameter estimation.* A recent article (10) showed how the response to a *single* dose may be utilized to evaluate all of the kinetic constants of a given patient needed to *predict* his or her future behavior. In the present study, a method is developed that meets *all conditions* for practical application by allowing implementation at *any time* after the initiation of typical hos-

pital therapy (daily and variable dosing) and by utilizing only the *routinely obtained and recorded* dose and prothrombin history data.

2. *Multiple-dose kinetics.* After obtaining estimates of the kinetic constants for a given patient, the doctor must estimate his or her response not only to the next few doses and, therefore, appropriately adjust their level, but also to longer range dose–effect relationships. General formulas that allow such estimates are then particularly convenient for quick computations. In the present study, such general formulas are derived for two classes of dosing schedules, namely, uniform (fixed dosing at fixed frequency); and quasiuniform (a single initial loading dose followed by a uniform dosing schedule). The results for some case computations are also presented for illustration.

THEORETICAL

Formulation—The differential equation that governs the time variation of prothrombin complex activity (P) is (2):

$$\frac{dP}{dt} = -m' \ln \frac{c_p(t)}{c_{pmax}} - k_d P \qquad \text{(Eq. 1)}$$

In this equation, k_d is the degradation rate constant of P, m' characterizes the synthesis rate of P, and c_{pmax} is the concentration of anticoagulant in plasma for which the synthesis rate of P is reduced to zero. Finally, $c_p(t)$ denotes the concentration of anticoagulant in the plasma at time t. Physical logarithms (ln) are utilized so that $m' = m/2.3$, with m as introduced previously (2). Following the standard procedure, P is expressed as percent of normal throughout this paper.

If c_{pmin} is defined as the minimum effective concentration, the steady-state [$(dP/dt) = 0$] value of P, P^0, in the absence of drug is given by:

$$P^0 = \frac{m'}{k_d} \ln \frac{c_{pmax}}{c_{pmin}} \qquad \text{(Eq. 2)}$$

To a good approximation (2), the absorption of oral anticoagulant may be considered instantaneous, while its removal (*i.e.*, elimination) follows first-order kinetics, *i.e.*:

$$\frac{dc_p}{dt} = -k_r c_p \qquad \text{(Eq. 3)}$$

If at some given time, say $t = 0$, the values of c_p and P are known, say $c_p(0)$ and $P(0)$, then the values of $c_p(t)$ and $P(t)$ for any later time may be obtained by integration of Eqs. 1 and 3:

$$c_p(t) = c_p(0)e^{-k_r t} \qquad \text{(Eq. 4)}$$

$$P(t) = P(0)e^{-k_d t} - \frac{m'k_r}{k_d^2}\{1 - e^{-k_d t} - k_d t\} - \frac{m'}{k_d}\{1 - e^{-k_d t}\} \ln \frac{c_p(0)}{c_{pmax}} \qquad \text{(Eq. 5)}$$

Equation 5 applies only for as long as c_p is less than c_{pmax} and more than c_{pmin}, *i.e.*:

$$c_{pmin} \leq c_p(0)\, e^{-k_r t} \leq c_{pmax} \qquad \text{(Eq. 6)}$$

In case the lower bound is met, the integration of Eq. 1 should continue with $c_p = c_{pmin}$. In case the upper bound is met, the integration of Eq. 1 should continue after setting the first term on the right-hand side equal to zero [for as long as $c_p(t) \geq c_{pmax}$].

Estimation of Parameters—The kinetic constants, k_d, k_r, m', and c_{pmax}, that appear in Eq. 5 must be identified for the particular patient if this equation is to give predictive capability. In a typical hospital situation, the *daily* values of prothrombin complex activity are available, as well as the correspondingly administered doses of anticoagulant. Let P_i denote the value of P at the end of the ith day and c_{pi}^0 denote the increase in concentration (in milligrams per liter) corresponding to the amount of anticoagulant given at the end of the ith day. The following two points should be noted:

1. Day zero may be taken as any day within the therapy period. However, if the choice of the start of anticoagulant therapy is made, it would lead more quickly to reliable results. In any case, c_{p0}^0 should be taken as the *total* concentration (*i.e.*, drug initially present plus amount given at time zero).

2. A patient's blood sample for the determination of P is usually obtained in the morning while the anticoagulant is administered at about 1:00 p.m. However, the required value in the derivation is P_i, *i.e.*, the value of P at the same time that c_{pi}^0 is administered. This may easily be obtained by graphical interpolation (see *Results* section).

The method of parameter estimation is as follows. By applying Eq. 5 for the end of the 1st day ($t = 1$ day), an estimate of P_1 is given by:

$$P_1 \text{ (estimated)} = P_0 e^{-k_d} - E - F \ln \frac{c_{p0}^0}{c_{pmax}} \qquad \text{(Eq. 7)}$$

where, for brevity, we have set:

$$E = \frac{m'k_r}{k_d^2}\{1 - e^{-k_d} - k_d\} \qquad \text{(Eq. 8)}$$

$$F = \frac{m'}{k_d}\{1 - e^{-k_d}\} \qquad \text{(Eq. 9)}$$

This estimate must be compared with the experimental value P_1, the "error" given by:

$$\epsilon_1 = P_0 e^{-k_d} - E - F \ln \frac{c_{p0}^0}{c_{pmax}} - P_1 \qquad \text{(Eq. 10)}$$

By applying Eq. 5 over the 2nd day, together with the help of Eq. 4, an estimate of P_2 is given by:

$$P_2 \text{ (estimated)} = P_1 e^{-k_d} - E - F \ln \frac{c_{p0}^0 e^{-k_r} + c_{p1}^0}{c_{pmax}} \qquad \text{(Eq. 11)}$$

The error over the 2nd day is given by:

$$\epsilon_2 = P_1 e^{-k_d} - E - F \ln \frac{c_{p0}^0 e^{-k_r} + c_{p1}^0}{c_{pmax}} - P_2 \qquad \text{(Eq. 12)}$$

This procedure can be continued for any number, n, of days for which data P_i and c_{pi}^0 are available; the values of k_d, k_r, m', and c_{pmax} for which the overall error is minimized are then sought. One choice of a measure of the overall error is the sum of the squares of the error committed in each day. Clearly, other choices are possible. The problem is then to find values for k_r, k_d, m', and c_{pmax} that minimize:

$$\Phi \equiv \sum_{i=1}^{n} \epsilon_i^2 \qquad \text{(Eq. 13}a\text{)}$$

or:

$$\Phi \equiv \sum_{i=1}^{n} (P_{i-1}^2 e^{-2k_d} + P_i^2) + nE^2 + F^2 \sum_{g=0}^{n-1} \ln^2 \sum_{g=i+j}^{i,j\geq 0} (c_{pi}^0/c_{pmax})e^{-ik_r} + 2F \sum_{g=0}^{n-1} [E - P_g e^{-k_d} + P_{g+1}] \ln \sum_{g=i+j}^{i,j\geq 0} (c_{pi}^0/c_{pmax})e^{-ik_r} + 2E \sum_{i=1}^{n} (P_i - P_{i-1}e^{-k_d}) - 2e^{-k_d} \sum_{i=1}^{n} P_i P_{i-1} \qquad \text{(Eq. 13}b\text{)}$$

The notation $\Sigma_{g=i+j}^{i,j\geq 0}$ means to form the indicated sum with all possible combinations of positive or zero i and j but such that $i + j$ equals the current value of g. As an illustration, the expression for Φ is given in the *Appendix*, without the summation notation, for the case of $n = 3$.

A large number of search methods may be applied to find the set of constants that minimizes Φ. However, since upper and lower

bounds on the possible values of them are available (*i.e.*, for the commonly utilized warfarin, $0 < k_r < 1, 0 < k_d < 5, 10 < m' < 100$, and $1 < c_{p\max} < 20$ constitute ranges within which almost certainly the constants of any individual must lie; as more experience is gained, revision of these bounds might become evident), the complete scan by evaluating Φ for all possible combinations of these parameters within the range of their expected values provides the most straightforward procedure for choosing the set that minimizes the overall error (Φ). This particular technique was utilized for the calculations presented in this paper. Some operational details for its implementation are given in the *Results and Discussion* section.

Naturally, a larger value of n yields a more reliable and precise evaluation of the kinetic constants. In principle, a minimum value of $n = 2$ seems adequate for a tentative first estimate. As more data become available during therapy, the minimization of Φ should be repeated for continuously improving all previous estimates.

General Solutions—First consider a quasiuniform dosing schedule. An initial ($t = 0$) loading dose corresponding to an increase in concentration of $c_{p0}^{(l)}$ is given and is followed by maintenance doses of fixed magnitude equivalent to $c_{p0}^{(m)}$. The time interval between dosing is kept fixed at τ days. Usually $\tau = 1$ day for anticoagulant therapy, but the more general case is considered where τ is arbitrary. No drug is present in the plasma previous to the administration of the loading dose, and the initial value of P (steady-state value) is P^0. By successive application of Eqs. 4 and 5 and generalization, the value of P is obtained at the end of the nth period (each of length τ). This value is denoted by $P_n(\tau)$ and is given by:

$$P_n(\tau) = P^0 e^{-nk_d\tau} - \frac{m'k_r}{k_d^2}(1 - e^{-k_d\tau} - k_d\tau)S_d^{(n)} - \frac{m'}{k_d}(1 - e^{-k_d\tau})R_n(\tau) \quad \text{(Eq. 14)}$$

where:

$$R_n(\tau) = \ln\left\{\left[\frac{c_{p0}^{(m)}}{c_{p\max}}\right]^{S_d^{(n)}} \lambda_r^{(n)}[\lambda_r^{(n-1)}]^{e^{-k_d\tau}}[\lambda_r^{(n-2)}]^{e^{-2k_d\tau}} \ldots [\lambda_r^{(1)}]^{e^{-(n-1)k_d\tau}}\right\} \quad \text{(Eq. 15)}$$

and:

$$\lambda_r^{(n)} = S_r^{(n)} + \left(\frac{c_{p0}^{(l)}}{c_{p0}^{(m)}} - 1\right)e^{-(n-1)k_r\tau} \quad \text{(Eq. 16)}$$

$$S_r^{(n)} = \sum_{j=0}^{n-1} e^{-jk_r\tau} \quad \text{(Eq. 17a)}$$

$$S_d^{(n)} = \sum_{j=0}^{n-1} e^{-jk_d\tau} \quad \text{(Eq. 17b)}$$

The drug concentration at the end of the nth period and just after the administration of the $(n + 1)$st dose is given by:

$$c_{pn}(\tau) = (c_{p0}^{(l)} - c_{p0}^{(m)})e^{-k_r n\tau} + c_{p0}^{(m)}S_r^{(n+1)} \quad \text{(Eq. 18)}$$

The variation of P within the $(n + 1)$st period is denoted by $P_{n+1}(t)$ and may be calculated from:

$$P_{n+1}(t) = P_n(\tau)e^{-k_d t} - \frac{m'k_r}{k_d^2}(1 - e^{-k_d t} - k_d t) - \frac{m'}{k_d}(1 - e^{-k_d t})\ln\frac{c_{p0}^{(m)}S_r^{(n+1)} + (c_{p0}^{(l)} - c_{p0}^{(m)})e^{-nk_r\tau}}{c_{p\max}} \quad \text{(Eq. 19)}$$

In Eq. 19, t measures time *within* a period, so $0 < t < \tau$.

Finally, with the use of Eq. 2, Eq. 14 may be written in a normalized form:

$$\frac{P_n(\tau)}{P^0} = e^{-nk_d\tau} - \frac{1}{\ln(c_{p\max}/c_{p\min})}\left\{\frac{k_r}{k_d}(1 - e^{-k_d\tau} - k_d\tau)S_d^{(n)} + (1 - e^{-k_d\tau})R_n(\tau)\right\} \quad \text{(Eq. 20)}$$

From this last equation, it is seen that the decrease in P/P^0 is independent of m' and depends only on the dimensionless groups: τk_d, τk_r, $c_{p\max}/c_{p\min}$, $c_{p0}^{(m)}/c_{p\max}$, and $c_{p0}^{(l)}/c_{p\max}$. This observation might prove important not only for convenience of data (or calculation)

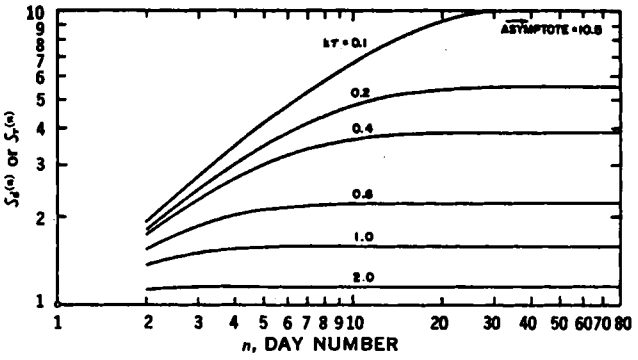

Figure 1—*Values of* $S_d^{(n)}$ *or* $S_r^{(n)}$ *for different values of* $k\tau$ *and* n.

presentation but also for achieving a more generalized approach to actual data analysis. This topic is under current investigation.

Clearly, the results for a uniform dosing schedule ($c_{p0}^{(m)}$) are contained in Eqs. 14–19 and may explicitly be obtained from them by simply letting $c_{p0}^{(l)} = c_{p0}^{(m)}$. This point is not further elaborated here because these results were also given explicitly previously (10).

It might appear that these equations are cumbersome to use for predictions over extensive periods of time (large n). Fortunately, however, they may be considerably simplified for large n to their asymptotic form:

$$P_\infty(\tau) = -\frac{m'k_r}{k_d^2}\left\{1 - \frac{k_d\tau}{1 - e^{-k_d\tau}}\right\} - \frac{m'}{k_d}\ln\frac{c_{p0}^{(m)}}{c_{p\max}(1 - e^{-k_r\tau})} \quad \text{(Eq. 21)}$$

Or, in normalized form:

$$\frac{P_\infty(\tau)}{P^0} = \frac{-1}{\ln(c_{p\max}/c_{p\min})}\left\{\frac{k_r}{k_d}\left[1 - \frac{k_d\tau}{1 - e^{-k_d\tau}}\right] + \ln\frac{c_{p0}^{(m)}}{c_{p\max}(1 - e^{-k_r\tau})}\right\} \quad \text{(Eq. 22)}$$

In this asymptotic region, the variation of P within any period is given by:

$$P_\infty(t) = P_\infty(\tau)e^{-k_d t} - \frac{m'k_r}{k_d^2}(1 - e^{-k_d t} - k_d t) - \frac{m'}{k_d}(1 - e^{-k_d t})\ln\frac{c_{p0}^{(m)}}{c_{p\max}(1 - e^{-k_r\tau})} \quad \text{(Eq. 23)}$$

Clearly, the asymptotic results apply for both uniform or quasiuniform dosing or for any case in which a constant dosing schedule is maintained for an extensive time. For convenience of computations, the values of the S's for different values of n and for the common values of $k_r\tau$ and $k_d\tau$ are given in graphical form in Fig. 1. Interpolation may easily be used for intermediate values of the arguments.

Provided the values of the kinetic constants for a particular individual have been determined, the equations presented in this sec-

Table I—Data for Patient W.F., Male, Age 58, Weight 88.9 kg. (196 lb.)

Date	Prothrombin Time, sec.	P, %	Sodium Warfarin Dose, mg.
8–13–71 (admitted)	—	—	20 (10:50 p.m.)
8–14–71	13.0	83 (9:00 a.m.)	10 (1:00 p.m.)
8–15–71	20.5	32 (9:00 a.m.)	5 (1:00 p.m.)
8–16–71	24.1	25 (9:00 a.m.)	5 (1:00 p.m.)
8–17–71	27.0	22 (9:00 a.m.)	3 (1:00 p.m.)
8–18–71	30.3	21 (9:00 a.m.)	0 (1:00 p.m.)
8–19–71	23.6	26 (9:00 a.m.)	5 (1:00 p.m.)
8–20–71	20.6	36 (9:00 a.m.)	5 (1:00 p.m.)
8–21–71 (discharged)	23.5	26 (9:00 a.m.)	4 (1:00 p.m.)

Table II—Data for Patient E.F., Female, Age 81, Weight 59.1 kg. (130 lb.)

Date	Prothrombin Time, sec.	P, %	Sodium Warfarin Dose, mg.
8–11–71 (admitted)	12.5	100 (9:00 a.m.)	0
8–12–71	12.1	97 (9:00 a.m.)	15 (1:00 p.m.)
8–13–71	14.1	62 (9:00 a.m.)	15 (1:00 p.m.)
8–14–71	28.8	22 (9:00 a.m.)	5 (1:00 p.m.)
8–15–71	32.3	16 (9:00 a.m.)	0 (1:00 p.m.)
8–16–71	27.1	22 (9:00 a.m.)	2 (1:00 p.m.)
8–17–71	25.5	23 (9:00 a.m.)	2 (1:00 p.m.)
8–18–71	24.0	28 (9:00 a.m.)	2 (1:00 p.m.)
8–19–71	21.0	31 (9:00 a.m.)	5 (1:00 p.m.)
.	.	.	.
.	.	.	.
.	.	.	.
9–4–71 (discharged)	25.0	24 (9:00 a.m.)	5 (9:00 a.m.)

tion enable one to *predict* the complete response [*i.e.*, variation of prothrombin complex activity (P) and drug plasma concentration (c_p) with time] to any choice of a loading dose ($c_{p0}^{(l)}$), maintenance dose ($c_{p0}^{(m)}$), and dosing interval (τ). Such capability would greatly facilitate the choice of an appropriate dosing regimen in accordance with the response sought.

RESULTS AND DISCUSSION

Application of Theory to Actual Hospital Cases—Recent, routinely taken, patient records from a Midwestern hospital were utilized for assessing the applicability of the theoretical results. The pertinent data arising from sodium warfarin therapy for two randomly selected cases are given in Tables I and II. For brevity, only the first 9 days of data are shown for Patient E.F. (Table II). As remarked later, the evaluations were found equally applicable to those data omitted from Table II (8–20 to 9–4). The dosing is illustrative of that presently utilized in practice (trial-and-error procedure). Data became available after the patient discharge so as to assure no feedback influence to patient care from the results, which are still to be considered experimental in nature. Spontaneous changes in P and interaction effects with other drugs are not unknown (11). From the data examined, such apparent effects were easily recognized and were not infrequently encountered. Presently, only qualitative information exists on such not-well-behaved cases. Those cases in which such effects were not pronounced enough to be recognizable by a qualitative examination of the data were characterized as well behaved. The two case studies reported here represent a random selection from the class of well-behaved cases.

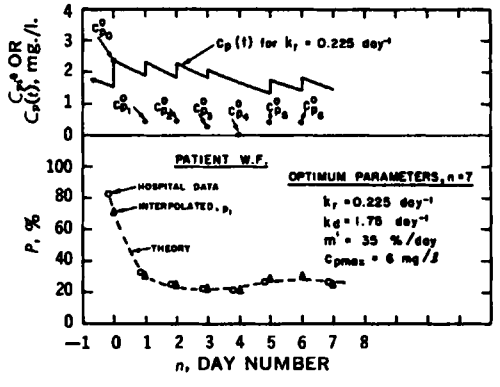

Figure 2—*Comparison of theoretical and experimental variation of* P *with time for Patient W.F. Upper half: magnitude of jumps in plasma level concentrations following each dose administration* (●). *The continuous line represents the resulting plasma concentration due to the combination of indicated drug administration and elimination (with a rate constant* k_r*). Lower half: comparison between experimental and predicted (with the kinetic constants as indicated) "prothrombin complex activity" variation with time.*

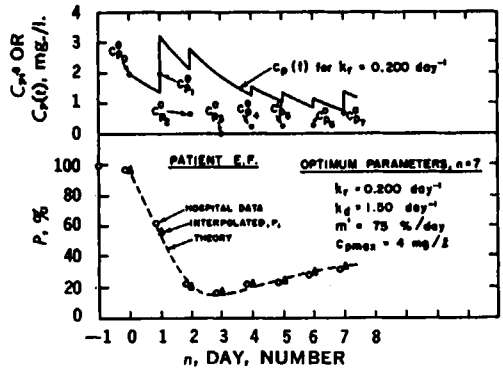

Figure 3—*Comparison of theoretical and experimental variation of* P *with time for Patient E.F.*

By taking the apparent volume of distribution as 0.13 l./kg. body weight (2), the values of $c_{p_i}^0$ were deduced and are shown in Figs. 2 and 3. Thus, c_{p1}^0, c_{p2}^0, c_{p3}^0, *etc.*, represent *increases* in plasma concentration due to dosing. On the same figures the actual data obtained for P are represented by circles. By drawing a smooth curve (not shown on figures) between these circles, the values of P_i were obtained by interpolation (triangles). Notice that for the case of Patient W.F., the absence of a P reading upon admission (P^0) necessitated taking the zero time for the evaluations as shown. The experimental point corresponding to the date 8–20 (n = 6) was omitted from Fig. 2 since it was abnormally high, and a check with other analyses recorded on this particular date indicated a systematic deviation in the P determination of an approximate magnitude of +10% of normal.

Minimizations of Φ for different values of n were performed (all having the same zero time), and the resulting best estimates of k_r, k_d, m', and c_{pmax} are summarized in Tables III and IV. The arithmetic for evaluating Φ as given by Eq. 13 was programmed for a digital computer. For each n, a sequential computation of Φ is afforded for all possible combinations of values of the parameters (k_r, k_d, m', and c_{pmax}) as they obtain values at prescribed increments within prescribed ranges. The expected ranges are given in the *Estimation of Parameters* section and were found to be indeed realistic. The increments utilized were as follows: 0.025 for k_r, 0.25 for k_d, 5 for m', and 1 for c_{pmax}. Clearly, a more refined mesh is possible but, in view

Table III—Optimum Kinetic Constants for Patient W.F.

n[a]	$\sqrt{\frac{\Phi}{n}}$[b]	k_r, day^{-1}[c]	k_d, day^{-1}[d]	m', %/Day[e]	c_{pmax}, mg./l.[f]
2	0.090	0.30	1.75	25	9
3	0.098	0.025	2.25	35	12
4	0.24	0.075	2.25	45	8
5	0.92	0.175	1.75	45	5
6	1.22	0.225	1.50	45	9
7	1.56	0.225	1.75	35	6

[a] Time length (in days) for which data were utilized in the computation. [b] Average error between theory and experiment. [c] Drug elimination rate constant. [d] Prothrombin complex activity degradation rate constant. [e] Constant characterizing synthesis rate of P, introduced in Eq. 1. [f] Concentration of anticoagulant in plasma for which the synthesis rate of P is zero.

Table IV—Optimum Kinetic Constants for Patient E.F.

n[a]	$\sqrt{\frac{\Phi}{n}}$[b]	k_r, day^{-1}[c]	k_d, day^{-1}[d]	m', %/Day[e]	c_{pmax}, mg./l.[f]
2	0.0028	0.075	1.25	65	4
3	1.03	0.375	1.25	75	3
4	1.83	0.200	1.50	80	4
5	2.08	0.200	1.50	75	4
6	1.88	0.200	1.50	75	4
7	1.76	0.200	1.50	75	4

[a–f] See footnotes in Table III.

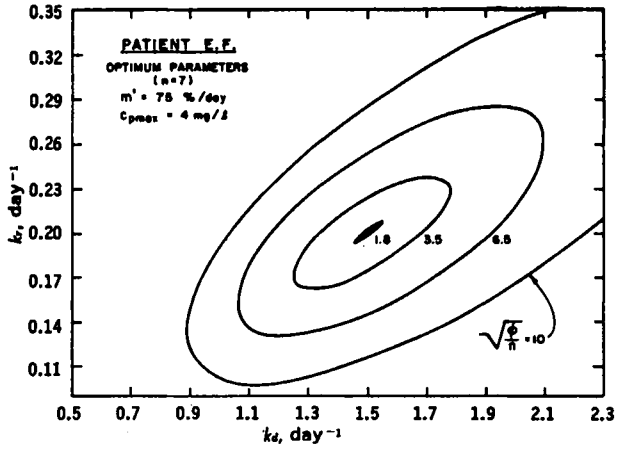

Figure 4—*Sensitivity plot for the determination of kinetic constants. The number on each ellipse indicates the maximum mean error expected between theory and experiment for* any *combination of* k_r *and* k_d *within the same ellipse and values of* m' *and* c_{pmax} *as shown on the figure.*

of the good comparisons with the experimental data thus obtained and the sensitivity properties discussed below, it appears unwarranted.

From the values of Φ thus obtained, the minimum is selected and the corresponding values of the k_r, k_d, m', and c_{pmax} then constitute the "optimum parameters." In Tables III and IV the value of $\sqrt{\Phi/n}$ is also shown since, in view of the manner in which Φ is being calculated, the former gives a measure of the "average" error between theory and experiment for the indicated choice of the kinetic constants. The value of $\sqrt{\Phi/n}$ reflects experimental (random) errors in the determination of P, as well as intrinsic variations in time of the kinetic constants that are not accounted for in the kinetic model. The detailed variation of $\sqrt{\Phi/n}$ with n seen in these tables is thus not significant. It is significant, however, that $\sqrt{\Phi/n}$ remains consistently small in all cases, a fact that testifies to both small errors in experimental data as well as to the suitability of the analytical technique and the accuracy of the kinetic model utilized. A minimal fluctuation (with increasing n) on the optimum values of the parameters is also observed. In view of the maintained smallness of the average error, this fluctuation is insignificant and the fit is always extremely good.

The comparisons between experimental data and prediction (dashed line), utilizing the optimum parameters obtained for $n = 7$, are shown in graphical form in Figs. 2 and 3. The theoretically obtained time variation of anticoagulant concentration for each case is also shown on the upper half of the figures with a continuous line. The see-saw appearance of these lines results from the consecutive

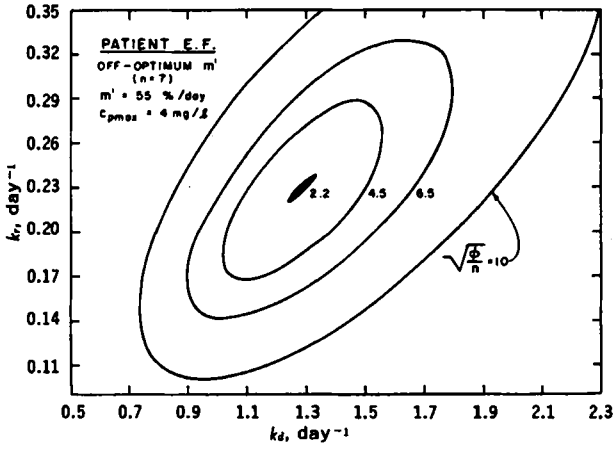

Figure 5—*Change in sensitivity and in "best" values of* k_r *and* k_d *for Patient E.F. resulting from a decrease of the optimum value of* m' *by 25%.*

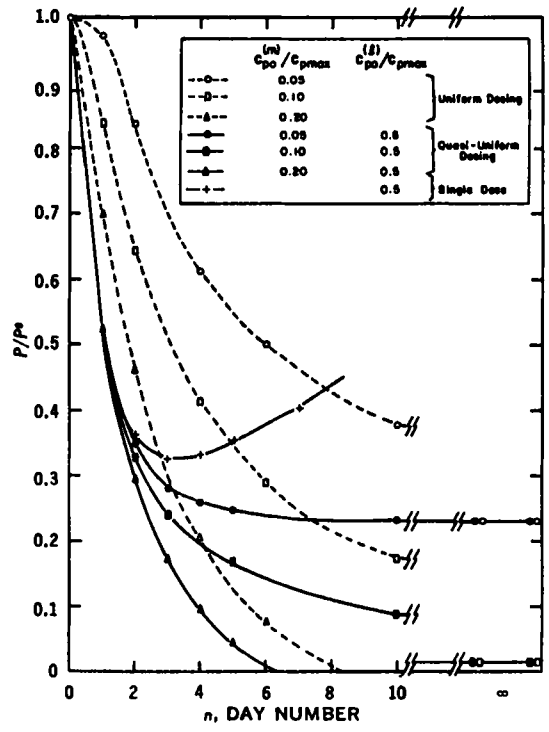

Figure 6—*Comparison in variation of* P/P^0 *with time for uniform and quasiuniform dosing and different dosing regimens.* $c_{po}^{(1)}$ *and* $c_{po}^{(m)}$ *represent the drug concentration jumps due to loading and maintenance dosing, respectively.*

application of drug elimination (with rate constant k_r) and a jump corresponding to an increase in concentration due to dosing (the magnitude of the jump is given by c_{pi}^0 as already discussed). With the exception of c_{pmax}, the values of the kinetic constants determined for these two cases are in the expected range as determined from previous laboratory studies (2–9). The values of c_{pmax} incorporate the variation of volume of distribution utilized from that of its actual value. In fact, it is significant that no precise knowledge of the volume of distribution is needed for application of this method, due to the fact that the formulas contain only the ratio c_{pi}^0/c_{pmax}. The suggested estimate of 0.13 l./kg. body weight (2) allows an evaluation of the c_{pi}^0's that is an approximation to the actual jump in concentration due to drug administration, and any variation of the utilized volume of distribution from the actual one of the particular individual is simply compensated for by a corresponding variation of the calculated c_{pmax} from its actual value. This interrelationship between volume of distribution and c_{pmax} is made more clear by means of Eq. 24:

$$\frac{c_{pi}^0}{c_{pmax}} = \frac{g_i/V}{c_{pmax}} = \frac{g_i}{(Vc_{pmax})} \qquad \text{(Eq. 24)}$$

where g_i is the dose (in milligrams) given the ith day.

The sensitivity of the fit between theoretical and experimental results is reflected in the variation of the value of $\sqrt{\Phi/n}$ relative to the minimum obtained for a corresponding variation in the parameters from their optimum values. The most comprehensive sensitivity illustration would require a five-dimensional diagram and would be more confusing than informative. However, the sensitivity to k_r and k_d is easily shown for fixed-optimum values of m' and c_{pmax} by plotting the values of $\sqrt{\Phi/n}$ for each combination of k_r and k_d as in Fig. 4. This diagram is termed a *contour* plot and is similar to those in cartography. Any ellipse is a locus of pairs of values (k_d,k_r) which give equal error as measured by $\sqrt{\Phi/n}$. The general shape of both figures indicates that the equations are not hypersensitive to small changes in these parameters. As a result, determined values of k_d and k_r are unique and significant. On the other hand, grossly horizontal or vertical contours would indicate a poorly behaved parameter evaluation; for example, a horizontal contour would signify that given a k_r, many possible values of k_d would yield an equally good

data fit. It is easily seen that any value of $0.19 < k_r < 0.21$ day^{-1} and $1.4 < k_d < 1.6$ day^{-1} would give essentially the same quality fit as in Fig. 3. Similar evaluation may be made for the sensitivity to m' and $c_{p\max}$ by plotting similar diagrams for fixed values of k_r and k_d. Although the sensitivity, in principle, changes from one patient to another, some broad conclusions may be drawn from case results as to which parameter is *usually* more important and needs the most precise evaluation.

Finally, to show the combined sensitivity to variations in m' and k_r and k_d, the value of m' was decreased by 25% from its optimum value and again the average error, $\sqrt{\Phi/n}$, was evaluated for various combinations of k_r and k_d. The results plotted in Fig. 5 indicate that this variation in m' from its optimum value resulted in a *new* "optimum" set of k_r and k_d as indicated. However, the error at this partial optimum is slightly larger than that at the true optimum. The overall relative sensitivity to k_r and k_d variations, reflected by the relative size of the areas enclosed by the lines of $\sqrt{\Phi/n} = 6.5$ for example, remained about the same.

Illustrative Calculations for Uniform and Quasiuniform Multiple Dosing—Computations of the normalized multiple-dose response were performed utilizing Eq. 20, and the results are presented in Fig. 6. These calculations are meant to be only illustrative and not typical or exhaustive. The following values of the parameters were utilized: $k_r\tau = 0.1$; $k_d\tau = 1.0$; $c_{p\max}/c_{p\min} = 26$; and $c_{p0}^{(m)}/c_{p\max} = 0.05$, 0.1, and 0.2 as indicated. If τ is selected different from 1 day, the "day number" should be interpreted as "period number" (each of length τ). For the quasiuniform dosing, the value of $c_{p0}^{(1)}/c_{p\max} = 0.5$ was utilized as a loading dose and was followed by uniform dosing with the parameters utilized before. The response to a single dose equivalent to $c_{p0}^{(1)}/c_{p\max} = 0.5$ is also included for comparison. The asymptotic values were obtained employing the asymptotic formula (Eq. 22). From these plots, the faster approach of a loading dose to asymptotic behavior is clearly illustrated, together with its dependence on the kinetic parameters. As more experience is gained with the practical applications and after a more definitive bracketing of the expected values of the kinetic parameters is established, accumulating graphical results such as those in Fig. 6 for an exhaustive number of cases might be a worthwhile undertaking. From those plots the response, $P_n(\tau)$, may be evaluated if the value of m' is known (for then P^0 may be calculated from Eq. 2).

SUMMARY AND CONCLUSIONS

A mathematical technique was presented for estimating the kinetic parameters that control patient response to oral anticoagulant administration. The technique utilizes only routinely obtained and recorded data such as dose magnitude and prothrombin times. It is possible to apply during any stage of therapy and to gain predictive capability from data covering the measured response over a minimum period of 2 days. The applicability of the technique was demonstrated by direct comparison with two actual patient records. The numerical evaluation required is only minimal, and the sensitivity of the results was illustrated by two examples.

Spontaneous changes and interaction effects are outside the scope of the presently proposed analytical technique. However, it does provide the means to exploit a large volume of hospital records and thus attempt to correlate the variation of the kinetic constants with disease states or to establish the onset (and hence the cause) of other drug interactions and spontaneous changes.

Finally, formulas were included for convenient computations of long-term responses to uniform or quasiuniform dosing.

APPENDIX

From Eq. 13, with $n = 3$, the following explicit form of Φ is obtained:

$$\Phi = e^{-2k_d}(P_0^2 + P_1^2 + P_2^2) + (P_1^2 + P_2^2 + P_3^2) + 3E^2 + F^2\{\ln^2[c_{p0}^0/c_{p\max}] + \ln^2[(c_{p0}^0/c_{p\max})e^{-k_r} + (c_{p1}^0/c_{p\max})] + \ln^2[(c_{p0}^0/c_{p\max})e^{-2k_r} + (c_{p1}^0/c_{p\max})e^{-k_r} + (c_{p2}^0/c_{p\max})]\} + 2F\{(E - P_0e^{-k_d} + P_1)\ln[(c_{p0}^0/c_{p\max})] + (E - P_1e^{-k_d} + P_2)\ln[(c_{p0}^0/c_{p\max})e^{-k_r} + (c_{p1}^0/c_{p\max})] + (E - P_2e^{-k_d} + P_3)\ln[(c_{p0}^0/c_{p\max})e^{-2k_r} + (c_{p1}^0/c_{p\max})e^{-k_r} + (c_{p2}^0/c_{p\max})]\} + 2E(P_1 + P_2 + P_3) - 2Ee^{-k_d}(P_0 + P_1 + P_2) - 2e^{-k_d}(P_1P_0 + P_2P_1 + P_3P_2) \quad \text{(Eq. A1)}$$

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