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PREDICTING ORAL ANTICOAGULANT RESPONSE USING A PHARMACODYNAMIC MODEL

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We developed a pharmacokinetic and pharmacodynamic model of warfarin absorption, metabolism, and anticoagulant action appropriate for guiding anticoagulant therapy. The model requires only two independently adjustable parameters to describe warfarin's effect on individual patients. For any given individual, these parameters are rapidly and inexpensively identified using a computer program based on the model. Test data were generated by superimposing Gaussian noise on dose-response curves calculated with the model. Then the computer program was applied to the test data. Future prothrombin complex activities (PCA's) and maintenance doses were predicted accurately early in the course of drug administration. In addition, the program accurately predicted PCA response in two groups of normal volunteers.

INTRODUCTION

Oral anticoagulants such as sodium warfarin are used in the treatment of several serious disorders such as thrombophlebitis and pulmonary embolism, as well as following some types of cardiac surgery. The use of these drugs is

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complicated by wide variations in individuals' responses to anticoagulants, which can lead to periods of underdosing and increased risk of thrombosis, or of overdosing and increased risk of hemorrhage. Although attempts have been made to estimate warfarin maintenance doses on the basis of such characteristics as body weight (9), there is no simple laboratory test or physical measurement that will provide a reliable estimate of a patient's maintenance dose prior to beginning treatment. Since the maximal effect on the prothrombin complex activity (PCA) of a single warfarin dose occurs 36 to 54 h after the drug is given, the effects of daily doses are cumulative and difficult to predict intuitively.

Methods for initiating oral anticoagulation should minimize the time required to achieve steady-state PCA values within the therapeutic range (here considered to be 20% to 30% of control), while protecting the patient from possible complications of drug therapy. In attempting to achieve this goal, a wide variety of approaches to initiating anticoagulation have been suggested. Initial doses have ranged from a very large (up to 60 mg) loading dose on the first day of therapy to initial doses much nearer the expected maintenance dose (usually less than 10 mg/day). The diversity of recommendations underscores the difficulty which the physician faces in initiating therapy with warfarin. Even after the more difficult initial anticoagulation has been achieved, most investigators have been able to maintain patients within the desired PCA range only 50% to 70% of the time (1, 10, 14, 17).

To more safely and systematically estimate the dose of anticoagulant which should be given, several investigators developed theoretical models of anticoagulant physiology and computer programs for assisting the clinician in prescribing proper warfarin doses (11, 15, 18, 20). Sheiner (18) modeled the kinetics of warfarin absorption and elimination by the equation

$$Q(t) = \sum_{i=1}^{n} C_i \exp[-k_e(t-t_i)], \tag{1}$$

where

$Q(t)$ is the total body warfarin (mg),
k_e is the elimination rate constant for warfarin (day^{-1}), and
C_i is the dose of warfarin (mg) given at time t_i.

The effect of warfarin on the prothrombin complex activity P was described by the equations

$$\begin{aligned} dP/dt &= -k_p P + (1 - sQ[t])\, S_m && \text{if } 1 - sQ[t] \geqslant 0 \text{ and } P < 100 \\ dP/dt &= -k_p P && \text{if } 1 - sQ[t] < 0 \text{ or } P = 100, \end{aligned} \tag{2}$$

where

k_p is the prothrombin complex degradation rate constant ($days^{-1}$),

S_m is the maximum rate of prothrombin complex synthesis (percent/day), and
s is a sensitivity constant (mg^{-1}).

Theophanus (20) used the same model as Sheiner for warfarin absorption and elimination, but modeled the effect of warfarin on the prothrombin complex activity as

$$dP/dt = -S_m \ln(Q/Q_{max}) - k_p P, \quad (3)$$

where Q_{max} is a concentration of warfarin which produces total inhibition of prothrombin complex synthesis. Both Sheiner and Theophanus incorporated their models into computer programs for predicting the response of patients to anticoagulant drugs.

However, these models suffer from serious drawbacks. Although the expression used for the absorption and elimination of the drug appears to be reasonable, the representations for the effect of warfarin on prothrombin complex synthesis do not arise naturally from the known biochemical mechanism of warfarin's effect. Sellers and Koch-Wesser (16) have suggested that inhibition of active prothrombin complex synthesis is best described by an enzyme-substrate model, and hence a Michaelis-Menten type of equation. This suggestion is consistent with the known mechanism of warfarin's action—competitive inhibition of the conversion of descarboxy-prothrombin to prothrombin (19). In addition, Sheiner and Theophanus both postulate that there is a warfarin dose that completely inhibits prothrombin complex synthesis. One would not expect the existence of such a maximum dose if prothrombin complex synthesis is inhibited by a mechanism described by either a competitive or a noncompetitive enzyme-substrate model. Furthermore, Theophanus' model requires the existence of a minimum effective dose, which is also unrealistic if warfarin acts as a competitive inhibitor.

In this paper we present an alternative representation of warfarin pharmacodynamics that corresponds more closely than models presented previously to the known physiologic systems. The model serves as the basis for an algorithm for computer-assisted anticoagulation that is simple enough to be implemented on a laboratory computer. The algorithm requires only the patient's warfarin dosage and prothrombin response history. It

1. identifies, using a nonlinear least squares method, the important parameters determining the patient's response to sodium warfarin,
2. predicts the patient's response to possible future doses of the drug,
3. suggests a dosage of drug to be given the next day to achieve appropriate levels of anticoagulation, and
4. gives a graphical display of the patient's responses to warfarin to date.

THE WARFARIN MODEL

We assume that warfarin is administered orally at times t_1, t_2, t_3 . . . t_n and is absorbed from the gastrointestinal tract into the circulation according to the equation

$$dG/dt = -k_g G + D(t), \tag{4}$$

where

$D(t) = C_i \delta (t - t_i), i = 1, 2 \ldots n,$
$\delta(t - t_i)$ is Dirac's delta function,
C_i is the dose (mg) of warfarin given at time t_i,
k_g is the rate constant for warfarin absorption (day^{-1}),
n is the total number of doses that have been given,
G is the amount of drug in the gastrointestinal tract (mg).

The nongastrointestinal total body warfarin content Q should obey the equation

$$dQ/dt = k_g G - k_e Q, \tag{5}$$

where k_e is the warfarin elimination rate constant.

Since the absorption of warfarin is very rapid, this model is essentially equivalent to that utilized by both Sheiner and Theophanus for warfarin absorption and elimination. Equations 4 and 5 may, however, also describe the pharmacokinetics of drugs which are not so rapidly absorbed, such as dicumeral.

The prothrombinemic response to drug is given by

$$dP/dt = S_m (1 - wQ/[wQ + k_m]) - k_p P, \tag{6}$$

where

w is the free fraction of warfarin divided by the distribution volume ($liter^{-1}$),
S_m is the maximal rate of prothrombin complex synthesis (percent per day),
k_p is the prothrombin degradation rate constant ($days^{-1}$),
k_m is a Michaelis constant (mg/l), and
P is the prothrombin complex activity (PCA).

At time $t = 0$, $Q(t) = G(t) = 0$ and $P(t) = P_0$, the measured initial prothrombin complex activity.

This equation differs considerably in both origin and effect from that used by previous workers (11, 15, 18, 20). It arises naturally from the assumption that warfarin exerts its effect by competitive inhibition of vitamin K utilized in the prothrombin carboxylation reaction. One need not assume values for

minimally or maximally effective concentrations of drug, and the equation is continuous for all drug concentrations.

At time $t = 0$, there is no warfarin present ($Q = 0$) and the system is expected to be at steady state. It follows from Eq. 6 that

$$S_m = k_p P_0. \tag{7}$$

Since there is no evidence that the presence of warfarin changes the rate of prothrombin complex degradation under normal conditions, the factor $k_p P_0$ may be substituted for S_m in Eq. 6, yielding

$$dP/dt = k_p P_0 (1 - wQ/[wQ + k_m]) - k_p P. \tag{8}$$

The sensitivity of the prothrombin complex activity, as given by Eq. 6, to the parameters k_g, k_p, k_e, k_m, w, and P_0 was tested by determining the behavior of $P(t)$ for many combinations of the parameters. Analysis of the results indicates that the prothrombin response $P(t)$ as given by the model is particularly sensitive to k_e and k_m over all ranges of P, and to P_0 when P is large. $P(t)$ is relatively insensitive to changes in k_g, k_p, and w, within the ranges normally found in patients anticoagulated with warfarin (10). This probably results less from the innate sensitivity of the model than it does from the fact that the inherent biological variability of the absorption rate constant k_g, the binding constant w, and the initial prothrombin activity P_0 are low. Nevertheless, this has important consequences in the selection of a dosage recommendation algorithm, as it is clearly most important to assure rapid identification of the more important parameters, even if this means that no attempt is made to accurately identify the less important ones. We are thus able to reduce the complexity of the model by proceeding as follows:

1. The value for P_0 is measured before anticoagulation is begun.
2. The constant k_p is assumed to be 0.9/day, nearly the same as that found by Levy *et al.* (7). Hence

$$S_m = 0.9 P_0. \tag{9}$$

3. Since the value of k_g has little importance, total warfarin content is estimated from Eq. 1 rather than from Eqs. 4 and 5.
4. The constant w is assumed to be 0.01 (16).

Thus only the two unknown parameters to which the model is particularly sensitive, k_e and k_m, must be identified in order to predict response to anticoagulants. This is advantageous, since these parameters can be identified more rapidly than they could be if a greater number of parameters were present. In addition, computation costs are reduced greatly.

If k_m, the Michaelis constant, represented simply the competitive inhibition of a single prothrombin complex carboxylation enzyme, it might not

be expected to vary from patient to patient. This parameter varies considerably among patients since it represents inhibition of several enzymatic processes, and is also affected by transport of warfarin into the compartment where prothrombin complex is synthesized.

IMPLEMENTATION OF THE MODEL

Implementation of the model for the purposes of predicting anticoagulant response and recommending warfarin doses is accomplished easily. Equation 1 is used without modification. Thus, given $Q(t)$, Eq. 8 may be integrated numerically in any of a number of ways. Although several methods were investigated, the backward Euler integration,

$$y_{i+1} = y_i + hf(y_{i+1}, t_{i+1}), \tag{10}$$

where

y_i is our approximation to $P(t_i)$,
$t_{i+1} = t_i + h$,
h is the step size, and
f is the expression for dP/dt (from Eq. 8),

was chosen because it was found to be reliable in the regions of the system corresponding to rapid decay of P (3). In addition it was capable of giving the required accuracy with extremely low computational costs. Roundoff error, which is the method's biggest liability, is not expected to accumulate sufficiently to affect adversely the overall performance during the time periods considered. Other integration methods could be employed, but would increase the computational expense without a clinically significant increase in accuracy.

We investigated several approaches to the parameter identification problem. Nonlinear Kalman filtering (4), for instance, may be used to estimate the patient's pharmacodynamic parameters while providing an estimate of their reliability. Maximum likelihood parameter estimation is potentially a viable alternative to the least squares approach. The patient parameters may generally be identified with greater precision using quite sophisticated iterative methods (5), nonlinear least squares methods (2), or Simplex (8) methods.

To minimize cost and to obtain increased flexibility in implementing the algorithm on minicomputers or microprocessors, we have adopted the following simple parameter identification procedure which is computationally less expensive than any of the above, and which, in spite of its great simplicity, is sufficiently accurate for clinical application.

Ten possible values of k_e and ten possible values of k_m are examined (Table 1). For each pair which is capable of yielding clinically reasonable maintenance doses (approximately fifty pairs), Eqs. 5 and 8 are integrated with the starting values

TABLE 1. Values for the Elimination Rate Constant k_e and the Michaelis Constant k_m Considered by the Parameter Identification Procedure

Elimination Rate Constant k_e (day^{-1})	*Michaelis Constant* k_m (mg/l)
0.25	0.0025
0.50	0.0050
1.00	0.0100
1.50	0.0250
2.00	0.0500
2.50	0.0750
3.00	0.1000
3.75	0.1500
4.50	0.2000
5.50	0.2500

$$Q(t = 0) = 0$$

$$P(t = 0) = P_0 \text{ (measured)}.$$

The appropriate values of k_e and k_m for the patient under consideration are selected by minimizing the nonlinear least squares function

$$R = \sum_{i=1}^{n} \Omega_i \left[P_i - P(t_i)\right]^2 / (P_i)^2, \tag{11}$$

where the P_i 's are values for the prothrombin complex activity measured at time t_i, and $P(t_i)$ is the value for P obtained by integrating Eqs. 1 and 8. The use of P_i in the denominator of Eq. 11 is appropriate if the standard deviations of the measurements P_i are a constant fraction of P. This appears to be approximately true over much of the range of P. The weighting factors Ω_i are given by

$$\Omega_i = (1/z)^{i-1} \tag{12}$$

for a chosen value of z between 0 and 1. This is equivalent to a time-exponential weighting in which the most recent measurements are weighted most heavily. Exponential weighting compensates for gross measurement errors, differences between the model and the physiologic system, and for changes in the patient's physiologic status after anticoagulation is begun.

DOSAGE SELECTION

After the values of k_e and k_m have been found, they may be used to predict patient response to a given dose of warfarin simply by integrating the above equations. They may also be used to suggest dosages for future days.

TABLE 2. Maximum Dose of Warfarin That Can Be Recommended by the Program

Days of Therapy	*Maximum Dose, mg*
1	5.0
2	5.0
3	7.5
4	10.0
5	15.0
>5	20.0

A rather simple approach to the dosage selection problem is taken. The maintenance dose required to keep the PCA as near to 25% as possible has been estimated in advance for all allowed combinations of the parameters k_e and k_m, and is selected from a dosage table in the program once k_e and k_m have been determined. The selected dose is intended to minimize the likelihood of the patient's prothrombin complex activity going outside the therapeutic 20% to 30% range once it has first been achieved, to minimize the number of dosage adjustments required during the course of anticoagulation, and to keep the time required to achieve anticoagulation acceptably low.

To be certain that only clinically useful dosages are profferred, dosages are restricted to amounts which can be given as a combination of 1.0 and 2.5 mg units. Since there is no advantage to using a loading dose, and since our experience suggests that the final maintenance dose for an average patient is likely to be about 5 mg/day, the dosage recommendation algorithm incorporates the restrictions shown in Table 2 on the maximum daily dose that the program may recommend. These limits are intended to minimize the risk of overanticoagulating a patient who actually requires a low loading and maintenance dose.

We have previously investigated more sophisticated approaches to dosage optimization. The objective for these optimization problems was to minimize the time required to first achieve a therapeutic PCA; the dosages recommended were constrained such that the predicted response did not go outside the therapeutic range after once achieving it. The difficulties with this approach were that the patient's pharmacodynamic parameters k_e and k_m were not identified with sufficient accuracy early in the course of therapy to make the recommendations during the early initial phases reliable, and that the dosage schedules calculated were clinically unacceptable as a result of the odd amounts of drug recommended (for example, 3.3 mg).

TEST OF THE PARAMETER IDENTIFICATION PROCEDURE

In order to gain an understanding of the speed and accuracy of the nonlinear least squares parameter identification procedure, the following test was carried out:

1. An initial prothrombin complex activity P_0 and constants k_e and k_m were selected. The appropriate "maintenance dose" was obtained from the dosage table and the response that would be expected if this dose were given every day from the start of therapy was calculated from the model. In this way an "ideal patient" response was calculated.
2. To simulate the effects of system and measurement noise, Gaussian random noise was superimposed on the response obtained above. For any given PCA, the standard deviation σ of this noise was given by $\sigma = \alpha P$, for $\alpha = 0.05$, 0.10, 0.15, 0.20, and 0.25. The points thus obtained, which represent the expected laboratory measurements of prothrombin complex activity for such a "patient," are referred to below as "PCA responses generated by the model."
3. The least squares identification procedure was employed, using the "noisy" data generated as described above, to find the "patient parameters" day to day. These parameters were then used to predict the "patient's" future responses to warfarin, referred to in Figs. 1 and 2 as PCA responses "predicted by the program."

In this way it was possible to determine how well the parameter identification procedure would function in the situation where the model describes exactly the physiologic response to warfarin, but where the data contain random noise resulting from changes in the "patient's" physiologic state as well as errors in the assessment of the PCA. The results obtained for some typical simulations are shown in Figs. 1 and 2. As expected, the predictions are much more accurate and parameter identification much more rapid when the system noise is small than when it is large, emphasizing the need

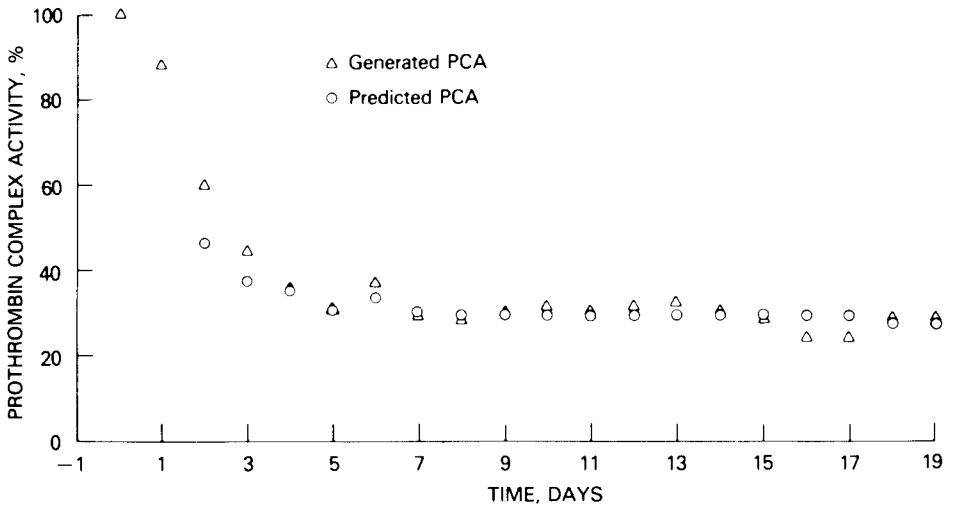

FIGURE 1. PCA responses generated by the model and predicted by the program for a simulation having a system noise level $\sigma = 0.10P$, warfarin elimination rate constant $k_e = 1.0$ day $^{-1}$, and Michaelis constant $k_m = 0.025$ mg/l.

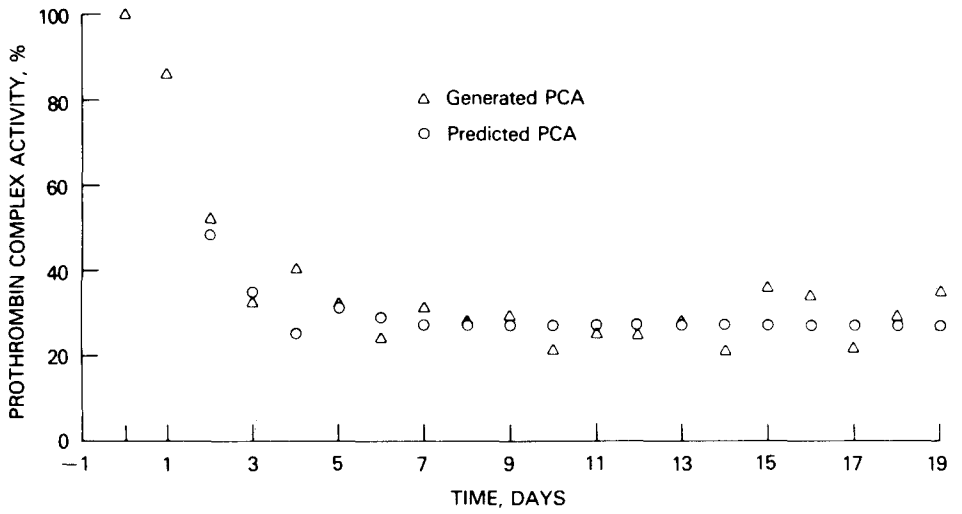

FIGURE 2. PCA responses generated by the model and predicted by the program for a simulation having a system noise level $\sigma = 0.015P$, elimination rate constant $k_e = 1.0$ day $^{-1}$, and Michaelis constant $k_m = 0.025$ mg/l.

for accurate and precise prothrombin activity measurements, particularly early in the course of therapy. Such measurements are seldom available. It was found that the quantity $[P_i + P(t_i)]/2$, where P_i is the measured prothrombin complex activity and $P(t_i)$ is the *a posteriori* estimate of the activity (from the model) provides a better estimate of the true activity (in this model system) than either P_i or $P(t_i)$ alone. The computer program makes this additional information available to the clinician, although we have no basis to assert that this estimate is superior to the measured prothrombin complex activity in clinical usage.

The simulations further substantiated the finding of the sensitivity analysis that errors in the initial estimate P_0 are important in the initial phase of anticoagulation (when P is large) but not later on. Finally, the analysis confirmed that the simple parameter identification procedure outlined earlier is sufficient to give reasonable predictions of the prothrombin complex response to oral anticoagulants, providing the model is valid and the measurement noise not excessive.

These simulations enable us to estimate the accuracy of predictions based upon the model, provided we can obtain an estimate for the system noise. In the following section we estimate this noise level based upon data from normal volunteers receiving constant doses of warfarin.

ESTIMATING THE SYSTEM NOISE

A model such as the one we have presented above is necessarily an approximation, as we use only a single variable, the prothrombin complex activity, to quantify the effects of warfarin on a very complicated clotting system in which a minimum of four clotting factors (Factors II, VII, IX,

and X) are affected by the presence of warfarin. In addition to this difficulty there are errors in the assessment of patient clotting status by PCA which complicate parameter identification and dosage estimation. These seemingly random errors we designate by the term "noise" together with fluctuations arising from such diverse sources as variation of the patient's body temperature, changes in the times at which warfarin is given and the PCA measured, and variation in the intervals between the time blood is drawn for PCA assessment and the time the laboratory test is performed. This short list is merely illustrative, and many other possible sources of noise exist. Data from a previous study (13) suggest that it is reasonable to consider this noise as Gaussian.

As suggested in the discussion above, a more detailed understanding of the effects of system noise on the rapidity with which parameter identification may be accomplished is important to ascertain the results which can be expected from, and the range of clinical applicability of, the pharmacodynamic model. We have previously estimated the intrinsic measurement noise of the Quick one-stage test to be over 5% of the measured PCA (15).

We have no *a priori* estimate for the magnitude of other contributions to the system noise, so only by a direct measurement can an overall estimate be obtained. The strategy used for this was as follows: From the values of the kinetic parameters k_e and k_m we have found in most patients, it seems likely that patients who have no physiologic instabilities and are receiving a constant dose of drug will reach a steady-state PCA by the end of ten days of anticoagulation. If this is true any variation in prothrombin complex activities found after ten days may be attributed to system noise. Thus we estimated the total noise as the standard error of all measurements taken after ten days, using data obtained in a previous study (13) in which normal volunteers received constant doses of warfarin for several weeks. There were six days available in the appropriate time range for each person in the data set. The mean PCA range for these ten patients ranged from 15% to 48%, and the noise thus calculated for each of the ten patients above, ranged from 10% to 20% of the prothrombin complex activity. Clearly, noise of this level limits our ability to identify accurately the pharmacodynamic parameters and predict prothrombin complex response to warfarin early in the course of therapy.

STUDIES OF PROGRAM EFFECTIVENESS IN PREDICTING PATIENT RESPONSE TO SODIUM WARFARIN

To evaluate the accuracy and effectiveness of the model of warfarin metabolism and action in predicting patient response to oral anticoagulants, a number of tests were performed using retrospectively obtained data. The first analysis was undertaken using data from O'Reilly and Aggeler (12), in which the same persons were, on different occasions, given both a large loading dose of sodium warfarin and several days of warfarin anticoagulation with much smaller doses (10 or 15 mg). A typical example of the

program's performance in predicting response to the bolus is shown in Fig. 3. The same subject's response to smaller daily doses is shown in Fig. 4. It is seen that in both cases satisfactory predictions of response are made after several days of warfarin administration, and that *a posteriori* least squares fits of the model to the patient data are good. For a given subject, there may be considerable differences between the values for the pharmacokinetic parameters k_e and k_m obtained after the single loading dose as compared to the values after multiple dosing. Although this finding may reflect differences in the pharmacokinetics and pharmacodynamics of the drug at high and low concentrations, it more likely reflects the effects of noise on the parameter identification procedure. If, instead of attempting to identify both k_e and k_m from the dosage response data, one sets k_e = 0.25, the k_m values are identified more rapidly, and converge to the same values whether the data is obtained after a large loading dose or a series of smaller maintenance doses. This appears to reflect the lack of significant (from the standpoint of this model) interindividual biologic variability of k_e.

The performance of the program was also evaluated in a number of normal volunteers who were given 7.5 mg of sodium warfarin each day for fourteen days (13). Although a somewhat longer time was required for adequate parameter identification, probably as a result of higher system noise, both predictions and retrospective fits, as illustrated in Figs. 5 and 6, are good.

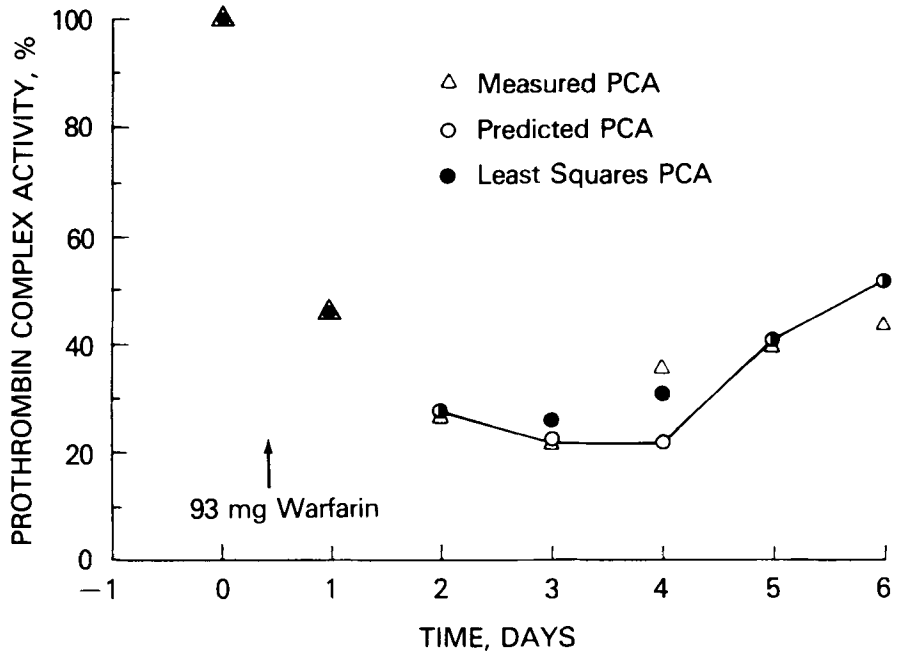

FIGURE 3. Measured and predicted PCA responses for normal volunteer (subject N-21) from O'Reilly and Aggeler (11) after receiving a 93 mg bolus on day 0 (retrospective study). The "least squares PCA" was calculated using the pharmacodynamic parameters identified on day 6.

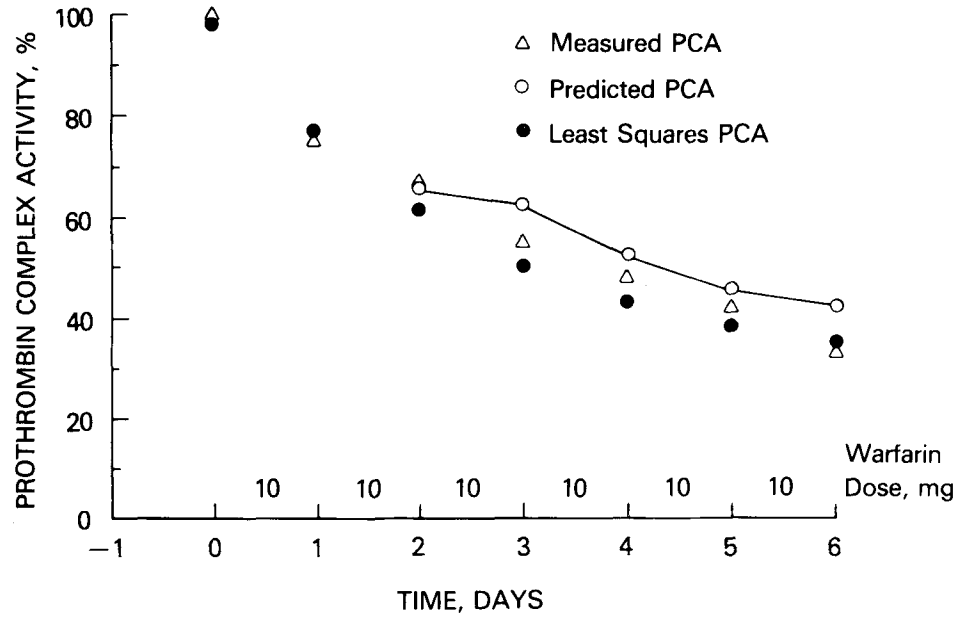

FIGURE 4. Measured and predicted PCA responses for subject N-21 from O'Reilly and Aggeler (12), given 10 mg warfarin daily for 6 days (retrospective study). The "least squares PCA" was calculated using the pharmacodynamic parameters identified on day 6.

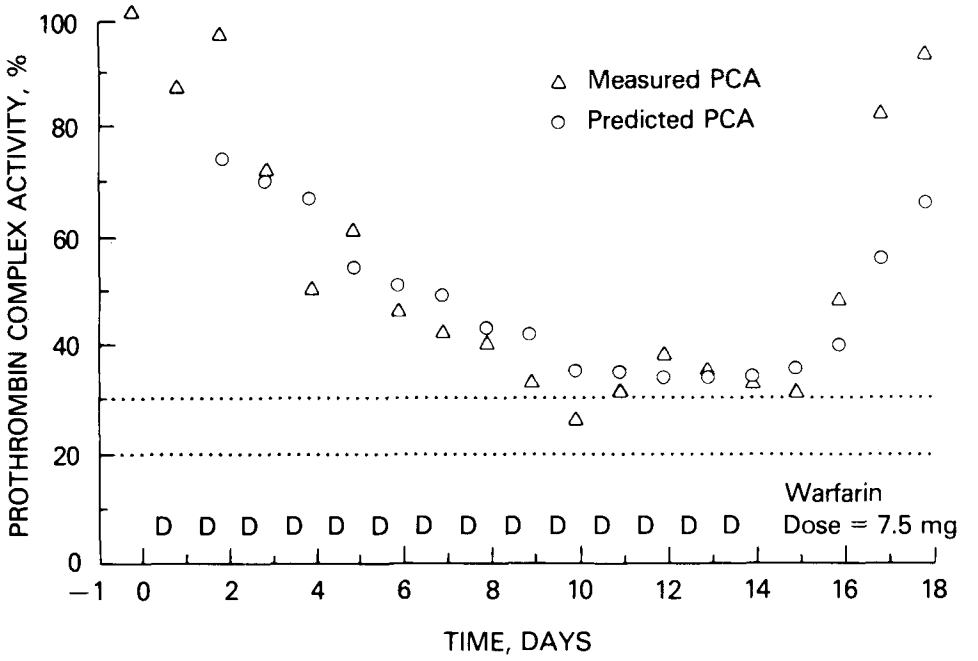

FIGURE 5. Measured and predicted PCA responses for normal volunteer J2 given 7.5 mg warfarin daily for 14 days (retrospective study). In this and subsequent figures the broken lines represent the upper and lower limits of PCA considered acceptable for oral anticoagulation at the University of Michigan Medical Center (UMMC).

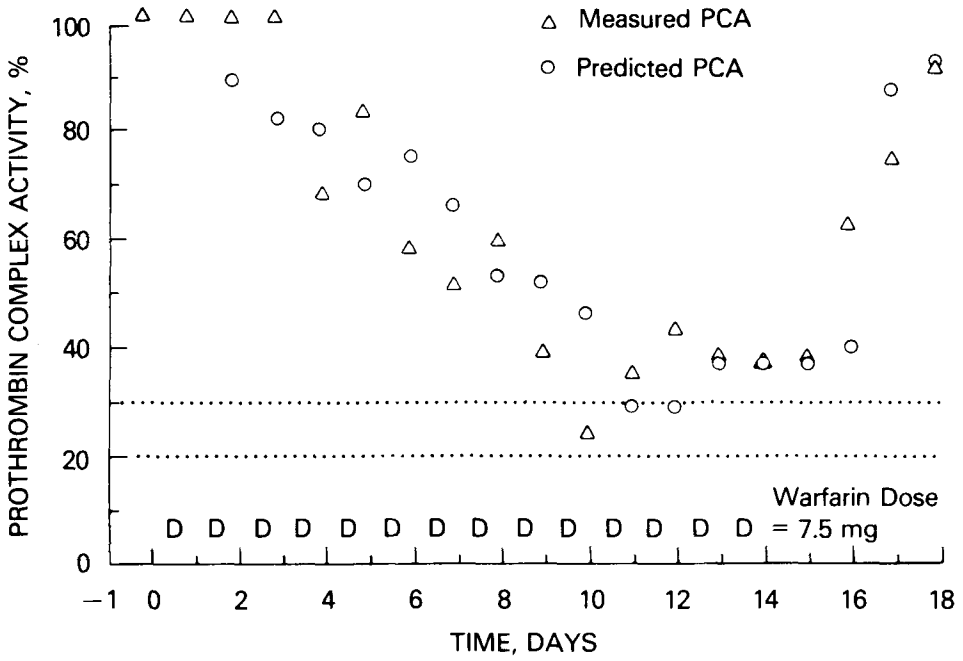

FIGURE 6. Measured and predicted PCA responses for normal volunteer given 7.5 mg warfarin daily for 14 days (retrospective study).

Finally, as a test of how well the program would perform in real patients in whom dosages vary from day to day and who might be expected to have somewhat less stable physiologic systems, a similar analysis was performed using data obtained from the hospital records of patients treated for a variety of medical and surgical conditions. Again the program performed adequately in most cases, as illustrated in Figs. 7 and 8.

Occasionally during the course of anticoagulation, the pharmacokinetic and pharmacodynamic parameters identified for an individual patient would change fairly drastically (see, for example, Fig. 9). In general this change of pharmacokinetic parameters was insignificant from the standpoint of maintenance dose estimation; the model appeared to fit the data reasonably well with either set of parameters (Fig. 10), and to make reasonable predictions of future PCA measurements. The reason for the difficulty in parameter estimation appears to be the inherently ill-posed nature of the parameter estimation problem for systems having equations reflecting Michaelis–Menten kinetics (21). Dose–response curves for markedly different parameter combinations are very nearly the same. This difficulty could be overcome by measurement of plasma warfarin concentrations.

DISCUSSION

We have presented a model of warfarin absorption, metabolism, and action which conforms well to known biochemical mechanisms of action and which can be used to predict accurately the response to warfarin once

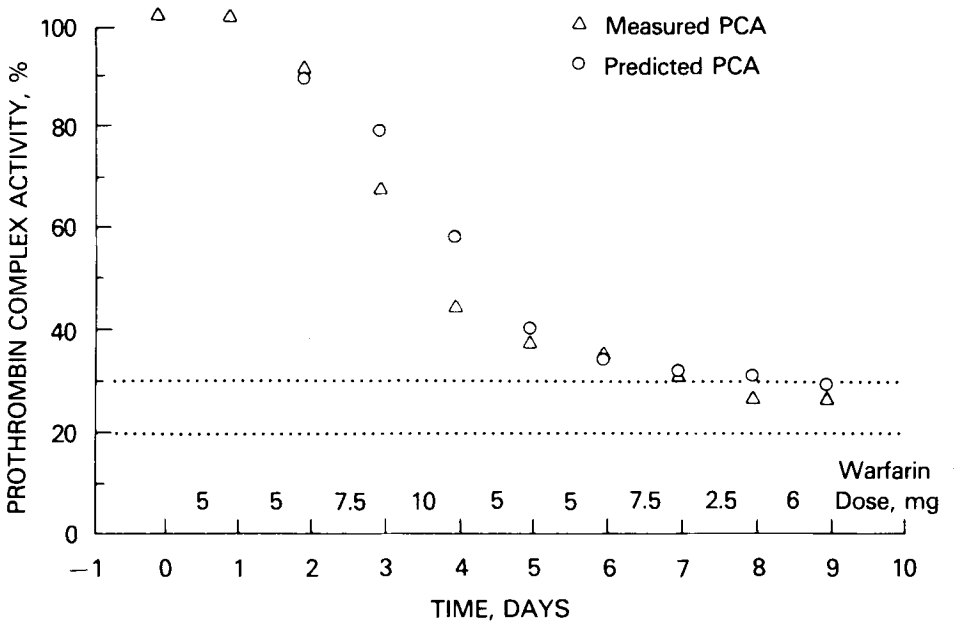

FIGURE 7. Measured and predicted PCA responses for patient DO studied at UMMC (retrospective study).

enough PCA and dosage data have been obtained. We believe the model to be more realistic than those presented by previous investigators. Only two parameters need be identified, using exceedingly simple and inexpensive

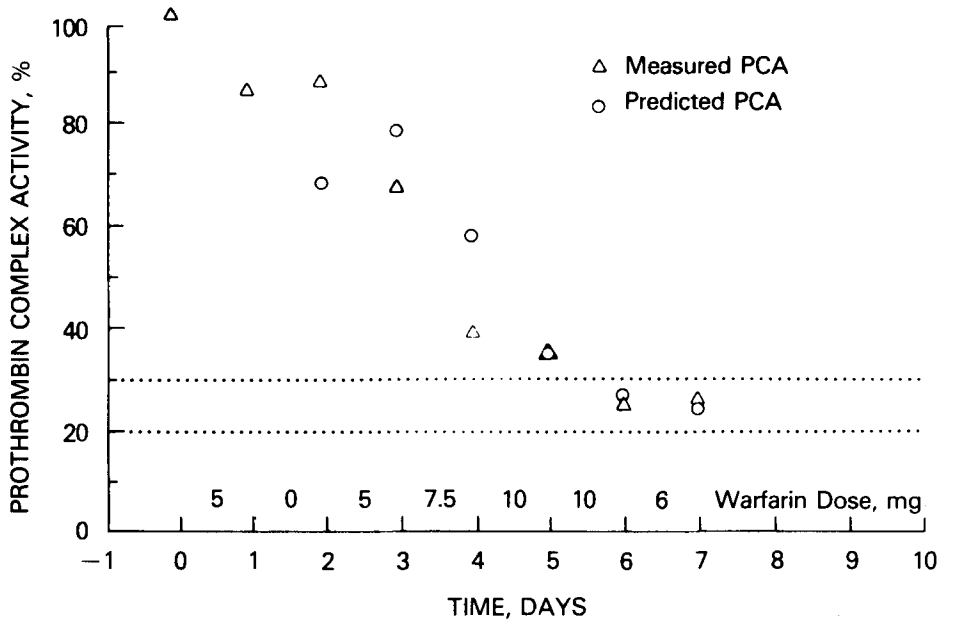

FIGURE 8. Measured and predicted PCA responses for patient KO studied at UMMC (retrospective study).

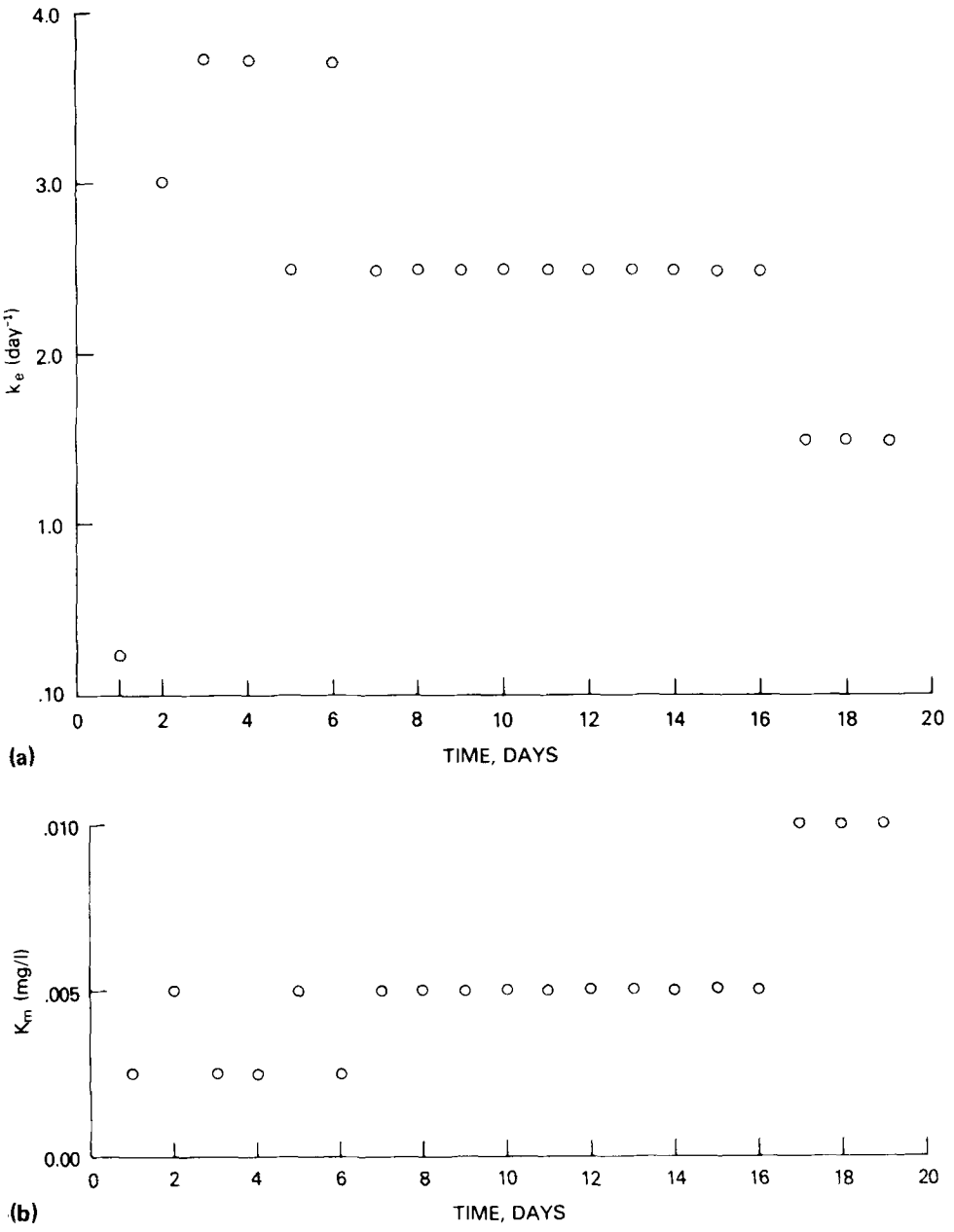

FIGURE 9. Values for the pharmacodynamic parameters identified by the program for "simulated patient" shown in Fig. 2. (a) Elimination rate constant k_e. (b) Michaelis constant k_m.

computational procedures, to predict accurately patient responses to the drug. Although the program's effectiveness in guiding therapy may be degraded if system noise levels are too high, we believe that it may be an effective and useful aid in guiding anticoagulant therapy in patients with a wide variety of medical and surgical problems.

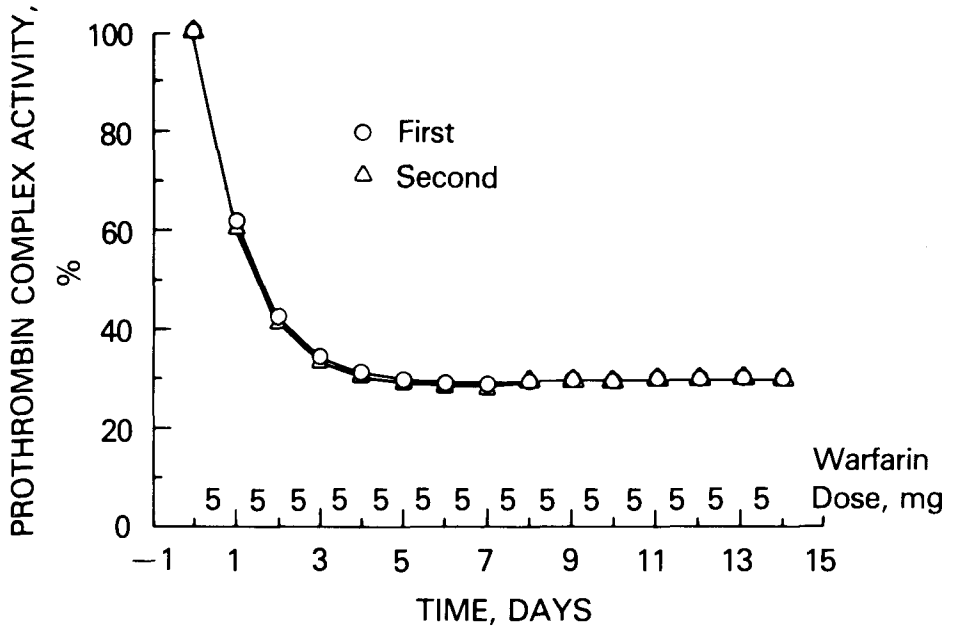

FIGURE 10. PCA response generated by the model for two widely different set of parameters. The first parameter set is k_e = 1.0 day^{-1} and k_m = 0.025 mg/l. The second parameter set is k_e = 0.50 day^{-1} and k = 0.075 mg/l.

Although a number of persons have reported the results of studies in which computer programs have been used to assist in long-term anticoagulation (6, 22), none has investigated whether patients anticoagulated with computer assistance remain within the therapeutic range for any greater percentage of the time than patients anticoagulated in the traditional way. The results of the retrospective investigation reported here were sufficiently encouraging that we have undertaken a prospective study of the program's effectiveness in guiding the initial phases of anticoagulation.

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