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Predictability of Warfarin Dose Requirements: Theoretical Considerations

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Abstract □ The theoretical basis of the predictability of warfarin maintenance dose requirements was evaluated using computer-generated hypothetical patient responses to a 10-mg/day "loading" dose regimen. Correlations between these responses and projected maintenance dose requirements were evaluated statistically, and a significant relationship was identified.

Keyphrases □ Warfarin—predictability of dose requirements, theoretical considerations, correlations between hypothetical patient responses and projected maintenance dose requirements □ Doses—predictability of warfarin requirements, theoretical considerations □ Maintenance dose requirements—predicting warfarin levels, theoretical considerations

Problems encountered in selecting an appropriate warfarin dosing regimen continue to represent a major obstacle to improvements in the quality and efficiency of oral anticoagulant therapy (1). Although the daily maintenance warfarin dose usually falls between 5.0 and 7.5 mg in large patient populations studied (2), wider variations in daily dose requirements are seen clinically, and the dose titration process used to determine this maintenance dose may be time consuming and relatively inefficient. The cost of added days of patient hospitalization required to select the maintenance dose may be significant.

Efforts to improve the efficiency of warfarin therapy have proceeded in two areas: (*a*) mathematical treatments describing the time course of warfarin's anticoagulant effects (3–5), and (*b*) clinical studies evaluating the predictability of steady-state warfarin dose requirements based on initial patient drug response (6–8). Two clinical investigations suggested a degree of predictability of anticoagulant maintenance dose requirements. A correlation was observed between the time required to achieve therapeutic anticoagulation (using a 15-mg/day "loading" dose regimen) and the maintenance warfarin dose finally required (6). Recently, a significant correlation between patient response to a specific loading dose regimen (10 mg/day for 3 days) and the maintenance dose required to achieve a desired steady-state degree of anticoagulation was demonstrated (7).

To evaluate the potential of these findings, the theoretical basis of observed correlations between loading and maintenance warfarin doses was investigated, using a previously described mathematical model for warfarin effect. The results of this evaluation and their clinical implications are described here.

BACKGROUND

Warfarin pharmacokinetics have been extensively investigated and are considered to be first order (3). They are described by:

$$C_p(t) = C_p^0 e^{-k_r t} \qquad \text{(Eq. 1)}$$

where $C_p(t)$ is the plasma drug concentration at any time t during a dosing interval, C_p^0 is the initial plasma concentration, and k_r is the first-order warfarin degradation constant.

Mathematical expressions describing the time course of the warfarin effect on coagulation after single or multiple doses were reported (5):

$$PCA(t) = P^0 e^{-k_d t} - \frac{mk_r}{(k_d)^2}(1 - e^{-k_d t} - k_d t)$$

$$- \frac{m}{k_d}(1 - e^{-k_d t})\ln\frac{C_p^0}{C_p^{max}} \quad (Eq. 2)$$

where PCA represents prothrombin complex activity, k_d is a first-order rate constant for prothrombin complex activity degradation, m is a constant relating the plasma warfarin concentration to clotting factor synthesis, and C_p and C_p^{max} are the actual plasma warfarin concentration and the plasma drug level at which the clotting factor synthesis rate reduces to zero, respectively.

In addition, the equation describing steady-state drug effects during uniform dosing schedules was derived (5):

$$PCA_{ss}(\tau) = [1 - k_d\tau/(1 - e^{-k_d\tau})]\frac{mk_r}{k_d^2}$$

$$- \frac{m}{k_d}\ln C_p^0(m)/[C_p^{max}(1 - e^{-k_r\tau})] \quad (Eq. 3)$$

where $PCA_{ss}(\tau)$ is the prothrombin complex activity at steady state at the beginning of a dosing interval, $C_p^0(m)$ is the plasma level at the beginning of a dosing interval at steady state after a maintenance dose, C_p^{max} is the plasma warfarin concentration above which all clotting factor synthesis ceases, and τ is the dosing interval. All other constants are as previously described.

Rearrangement of Eq. 3 produces an expression for the estimation of required maintenance doses needed to produce desired steady-state anticoagulant effects:

$$dose = exp\left[-PCA_{ss}(\tau) + \frac{mk_r}{k_d^2}[1 - k_d\tau/(1 - e^{-k_d\tau})]\frac{k_d}{m}\right]$$

$$\times [C_p^{max}(1 - e^{-k_r\tau})]V_d \quad (Eq. 4)$$

where V_d is the volume of distribution.

For calculation purposes, warfarin absorption after oral administration can be considered to be instantaneous and complete, obviating the need for a biexponential expression. The volume of distribution is considered to be 0.13 liter/kg (5).

EXPERIMENTAL

Equation 2 was used to generate a series of hypothetical patient responses to the administration of five consecutive daily 10-mg warfarin doses. A patient weight of 70 kg was arbitrarily selected. The case responses were produced by iterative substitution of sets of parameter values (k_r, k_d, m, and C_p^{max}) into the equations. The parameter ranges and increment sizes used in the computations are listed in Table I.

Estimated prothrombin complex activity levels were calculated at 18-hr intervals after each 10-mg dose. Projected maintenance doses required to achieve a desired therapeutic steady-state prothrombin complex activity level of 20% were calculated using Eq. 3.

After initial calculations, only parameter sets producing projected daily maintenance doses between 2.0 and 15.0 mg were used for correlation analyses with the patient response data.

The statistical correlations between the projected maintenance doses and the calculated prothrombin complex activity values after each 10-mg dose were computed[1]. All calculations were performed on a digital computer[2] using the PL/I language.

RESULTS AND DISCUSSION

A total of 914 hypothetical cases was evaluated. The mean prothrombin complex activity values observed after each dose and the respective ranges and standard deviations are shown in Table II. The mean projected maintenance dose was 6.9 mg/day (range of 2.0–15.0). This value is consistent with average daily doses reported previously (2).

Statistically significant linear correlations ($p < 0.0001$) were observed between calculated responses after each dose, or their logarithmic transforms, and the projected maintenance doses. These correlations, although significant, were relatively poor after the first dose ($r = 0.28$)

[1] Statistical Analysis System, Version 76.5, GLM Procedure.
[2] IBM 370/155, Triangle University Computation Center, Research Triangle Park, N.C.

Table I—Parameter Range and Increment Values Used in the Iterative Data Generation

Parameter	Upper Limit	Lower Limit	Increment Value
k_d, day^{-1}	3.5	0.5	0.5
k_r, day^{-1}	0.6	0.3	0.1
m	60.0	10.0	5.0
C_p^{max}, µg/ml	15.0	5.0	1.0

Table II—Mean Values and Ranges of Prothrombin Complex Activity as a Function of the Number of 10-mg Warfarin Doses Administered

Dose	Prothrombin Complex Activity, %		
	Mean	SD	Range
1	90.2	6.4	73.1–100.0
2	42.8	11.2	21.8–84.1
3	32.4	9.4	16.2–70.9
4	28.2	8.2	14.2–60.4
5	26.1	7.6	11.9–52.4

Table III—Correlation Coefficients between Projected Maintenance Dose Requirements and Predicted Loading Dose Response as a Function of the Number of Doses Administered

Dose	Correlation Coefficient r	
	Dose versus Prothrombin Complex Activity	Dose versus $\log_{10}$ Prothrombin Complex Activity
1	0.28	0.28
2	0.78	0.80
3	0.87	0.89
4	0.92	0.92
5	0.92	0.92

Table IV—Mean Projected Maintenance Dose as a Function of the Time Required to Achieve Therapeutic Prothrombin Complex Activity Levels ($\leq 35\%$)

Days	Dose, mg/day	Dose Range, mg/day	Cases
0–2	3.4	2.0–6.6	255
3–4	6.7	2.0–13.1	464
5 or more	12.0	5.0–15.1	195

but improved considerably. After the second dose ($r = 0.79$), this improvement was relatively asymptotic up to the fifth dose ($r = 0.92$). The values of the correlation coefficient, r, are given in Table III. There appears to be little difference in the correlations obtained using raw coagulation data or the logarithmic transform.

The observed correlation coefficient between the projected daily maintenance dose and the logarithm of the prothrombin complex activity, calculated 18 hr after the third 10-mg dose, was 0.89. This value is in very close agreement with the coefficient, 0.90, recently reported in a clinical investigation using experimental data for 34 patients. The clinical findings contained in that report may have sound theoretical support. Graphical illustration of the relationships between the projected maintenance doses and the responses observed after the third dose is provided in Fig. 1.

Another report (6) proposed a relationship between the number of days required to reach minimal therapeutic levels of anticoagulant effect (PCA $\leq 35\%$), using a fixed loading regimen (15 mg/day), and the maintenance warfarin dose finally required. This concept was evaluated using the hypothetical data generated from a 10-mg dosing regimen. The mean projected maintenance doses were calculated for three groups of response cases where: (a) a prothrombin complex activity of 35% was achieved after one or two doses, (b) a 35% level was achieved after the third or fourth dose, and (c) a 35% level was not achieved until at least the fifth dose (Table IV). As can be expected, the mean projected maintenance dose increased as the time required to achieve a therapeutic effect increased.

Many facilities currently assess warfarin effect by measurement of the prothrombin time and calculation of the prothrombin ratio (PR). To bring these findings into perspective in relation to the prothrombin ratio,
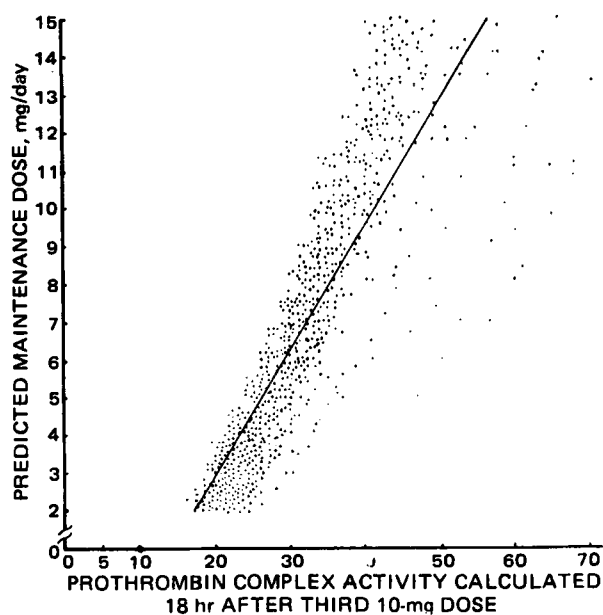
Figure 1—*Relation between projected maintenance warfarin dose and prothrombin complex activity value estimated 18 hr after the third 10-mg dose* $[y = 0.332 (PCA - 11.60), r = 0.89, and n = 914]$. *The solid line represents the best statistical fit line.*

a conversion between prothrombin complex activity and the prothrombin ratio proposed previously (4) can be used:

$$PR = \frac{(100/PCA) + 2.636}{3.636} \quad \text{(Eq. 5)}$$

With this expression, a stratified description of the relationship between ratio values observed after the third 10-mg dose and mean projected maintenance doses was produced (Table V). In addition, rough clinical approximations of maintenance dose requirements can be derived from Table IV. If a prothrombin ratio of 1.5 is achieved after the first or second dose, the daily maintenance dose required might approximate 4–5 mg. If three or four doses are required to achieve this ratio, 7.5 mg/day would be required. If five or more doses are needed, 10–15 (12.5) mg/day would be needed.

Any evaluation of these results must be considered carefully until more clinical data are available. Application of the mathematical concepts described here to individual patient situations should ideally be based on additional results of clinical studies. It has been shown that oral anticoagulants such as warfarin exert their pharmacological effects on prothrombin synthesis through inhibition of the regeneration of vitamin K_1 from its epoxide metabolite (8). Therefore, the anticoagulant action of warfarin depends not only on the drug concentration at its site of action but also on the concentrations of vitamin K_1 and vitamin K_1 epoxide in the body. Factors such as diet and concomitant drug therapy can influence these concentrations and coagulation, independently of warfarin concentration. Certainly, these results are based on conditions where

Table V—Projected Maintenance Dose Requirements as a Function of the Estimated Response to Three Daily 10-mg Doses

Prothrombin Ratio[a]	Mean Projected Maintenance Dose, mg/day	Maintenance Dose Range, mg/day
1.00–1.20	12.3	8.4–15.0
1.21–1.30	11.8	5.0–14.9
1.31–1.40	12.0	6.0–15.1
1.41–1.50	9.5	4.8–13.6
1.51–1.60	7.6	3.7–11.3
1.61–1.70	5.8	3.0–8.3
1.71–1.80	4.7	2.2–6.8
1.81–1.90	3.7	2.0–5.6
1.91–2.00	3.2	2.0–4.5
>2.00	2.6	2.0–3.8

[a] Ratio value estimated 18 hr after third 10-mg dose.

nonlinear alterations in warfarin effects do not influence patient response. Drug or dietary influences that might alter usual patient response are still relatively difficult to quantitate, and the need for routine measurement of the prothrombin ratio as a definitive indicator of warfarin effects is not in any way affected by these findings.

With further assessment and confirmation of the potential clinical validity of these results, more efficient, less time-consuming methods for initiating warfarin therapy might be developed. Previous clinical studies (6, 7) showed that adequate anticoagulation can be achieved with the use of a standardized loading dose regimen. In light of the results of those investigations and the data presented in this paper, there seems to be little justification for use of the erratic dosing patterns followed in the past when the initial administration of a relatively simple 10-mg/day regimen can provide a reasonably reliable indicator of maintenance drug needs. Any regimen used, however, should include daily monitoring of clinical coagulation parameters.

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