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Determination of kinetic parameters for prothrombin complex activity during initiation of anticoagulation

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SUMMARY

Objective: **A prospective determination of the kinetic parameters of prothrombin complex activity (PCA) during initiation of anticoagulation in seven adult patients (4 males and 3 females, age 62·9 ± 5·8 years, mean ± SD) receiving anticoagulant therapy with warfarin.**

Method: **All excluding one patient received a fixed daily dose of 5 mg warfarin over an initial 3 days. Three successive daily doses of warfarin were recorded, together with the corresponding PCA. The kinetic parameters for elimination of PCA during the initiation of anticoagulation were estimated from the log PCA–time plot with a 1-compartment model.**

Results: **The mean elimination rate constant (k_p) of PCA was 0·377 day^{-1} (range 0·242–0·588 day^{-1}) during initiation of anticoagulation. The coefficient of variation in k_p was about 28%, indicating the considerable inter-individual differences in PCA response to warfarin. The mean plasma half-life of PCA was 1·96 days. There were no significant relationships (by simple regression analysis) between k_p and cumulative warfarin doses per kg of body weight or age during initiation of anticoagulation.**

Conclusion: **The results suggest that for a 50% reduction of PCA, one would need about 2 days after initiation of anticoagulation.**

INTRODUCTION

Warfarin is an oral anticoagulant which is widely used in the treatment of thromboembolic disorders. Patients vary widely in the daily doses of warfarin which they require to produce similar anticoagulant effects (1). An estimation of warfarin maintenance doses is commonly based on a measurement of prothrombin complex activity (PCA) during the initiation of warfarin therapy (2). Detailed investigations on the kinetics of PCA are needed to predict the time course of changes in PCA during the initiation of oral anticoagulation therapy.

The clinical studies of PCA kinetics are sparse, and there is even less information on the kinetic parameters of PCA during the initiation of anticoagulation therapy. In this study, we prospectively determined the kinetic parameters of PCA during the initiation of anticoagulation therapy in patients receiving anticoagulant therapy after percutaneous transluminal coronary angioplasty with stent implantation. In addition, the effects of the warfarin dose or age on the kinetics of PCA were also determined.

METHODS

Subjects

Seven patients (4 males and 3 females) were studied (Table 1). The patients' ages ranged from 55 to 73 years (mean ± SD: 62·9 ± 5·8 years). All patients had been treated with warfarin as an anticoagulant, a preventive treatment for thromboembolic disease caused after percutaneous transluminal coronary angioplasty. No patients were given diets which would affect the pharmacodynamics of warfarin, as indicated in the manufacturer's package insert. Any patient with clinical or biochemical evidence of hepatic disease (a patient presenting with active hepatic disease or hepatic function tests which were greater than three times baseline) or cardiac failure, or who was receiving drugs known to alter the metabolism or plasma protein binding of warfarin (3), was excluded.

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Table 1. Patient characteristics

Patient no.	Sex	Age (years)	Weight (kg)	Serum creatinine (μmol/L)	AST* (U/L)	ALT† (U/L)	Serum albumin (g/L)
1	F	66	51·7	88	26	15	39
2	F	64	60·0	71	27	49	39
3	M	55	77·5	115	32	20	38
4	M	62	74·3	97	24	23	40
5	F	62	49·0	106	27	20	40
6	M	73	76·9	97	25	11	39
7	M	58	62·0	97	21	34	37
Mean		62·9	64·5	97	26	25	39
SD		5·8	11·9	18	3	13	1
Normal range				62–115	11–36	2–34	30–49

* AST: aspartate aminotransferase.
† ALT: alanine aminotransferase.

Dosing schedule of warfarin and determinations of prothrombin complex activity

In this study, PCA was used to characterize the patient's response to warfarin. Because the therapeutic target PCA was expected to be attained 2–3 days after starting warfarin treatment (2), three successive daily doses of warfarin were recorded, together with the corresponding PCA.

All patients received oral warfarin at approximately 21.00 hours during the study. Initial dosing schedules are presented in Table 2. All excluding one patient (no. 3) received a fixed daily dose of 5 mg warfarin during the first 3 study days.

Thromboplastin from rabbit brain–lung (Simplastin-Plus®; Organon Teknika Co., Tokyo, Japan) was used for PCA determinations. Plasma samples were analysed (Department of Clinical Laboratory, University Hospital) for PCA determinations. The PCA determinations were made daily at approximately 06.30 hours on 3 consecutive days after the initiation of anticoagulation therapy.

Calculations

The kinetic parameters for PCA elimination during the initiation of anticoagulation therapy in each patient were estimated from the log PCA–time plot with a 1-compartment model according to the following equations:

$$P = P_0 \bullet t\exp(-k_p t) \quad (1)$$

$$t_{1/2} = 0{\cdot}693/k_p \quad (2)$$

where P is the prothrombin complex activity (%) at time t (days) after the initiation of anticoagulation, P_0 is the prothrombin complex activity (%) before anticoagulation, k_p is the elimination rate constant (day^{-1}) of prothrombin complex activity during initiation of anticoagulation, and $t_{1/2}$ is the plasma half-life (days) of prothrombin complex activity during initiation of anticoagulation. The data obtained before and during anticoagulation therapy were fitted to eqn 1

Table 2. Dosing schedule of warfarin during initiation of anticoagulation therapy

Patient no.	Daily dose (mg)			Cumulative dose* (mg/kg)
	1st day	2nd day	3rd day	
1	5	5	5	0·290
2	5	5	5	0·250
3	6	4	3	0·168
4	5	5	5	0·202
5	5	5	5	0·306
6	5	5	5	0·195
7	5	5	5	0·242

* Values were calculated by dividing the sum of the three initial daily doses by body weight.

Table 3. Prothrombin complex activity (%) before or after initiation of warfarin therapy

Patient no.	Before	After initiation of therapy		
		1st day	2nd day	3rd day
1	123·5	48·8	23·6	43·1
2	139·5	44·0	31·8	41·5
3	124·9	53·8	50·0	40·0
4	133·3	70·7	56·7	48·7
5	125·2	70·9	35·0	22·3
6	169·2	80·0	58·8	58·3
7	122·2	59·4	62·8	53·6
Mean	134·0	61·1	45·5	43·9
SD	16·7	13·2	15·3	11·6

Table 4. Kinetic parameters for elimination of prothrombin complex activity during initiation of anticoagulation and coefficient of determination to evaluate a fit of the regression line for prothrombin complex activity vs. time

Patient no.	k_p* (day^{-1})	$t_{1/2}$† (days)	r^2‡
1	0·389	1.78	0·537
2	0·396	1.75	0·608
3	0·349	1.99	0·815
4	0·324	2.14	0·891
5	0·588	1.18	0·994
6	0·351	1.98	0·816
7	0·242	2.87	0·695
Mean	0·377	1·96	
SD	0·106	0·51	

* k_p: elimination rate constant of prothrombin complex activity.
† $t_{1/2}$: plasma half-life of prothrombin complex activity.
‡ r^2: coefficient of determination.

by the least-squares method. A fit of the regression line for log PCA vs. t was evaluated with a coefficient of determination (r^2).

The relationship between elimination rate constant for PCA and the cumulative warfarin doses during the initial 3 days of anticoagulation therapy was determined by simple regression analysis. The relationship between the elimination rate constant of PCA and patient age was also determined. P-values of less than 0·05 were considered to be statistically significant. The data analysis was performed using the StatView statistical package (Abacus Concepts, Berkeley, CA, U.S.A.).

RESULTS

The data for each individual patient for the changes of PCA before or after initiation of warfarin therapy are presented in Table 3. The PCA values tended to decrease with the progression of treatment. The PCA values before initiation of warfarin therapy ranged from 122·2 to 169·2% (mean 134·0%). The mean PCA values on each day after initiation of anticoagulation therapy were 61·1% (range 44·0–80·0%) on the first day, 45·5% (range 23·6–62·8%) on the second day, and 43·9% (range 22·3–58·3%) on the third day.

Only two patients (nos 1 and 5) were within our target range for PCA (20∼30%) by the third day. In all patients, a decline in PCA was observed on the first day after initiation of anticoagulation. However, in one of the patients (no. 7) the PCA values after initiation of anticoagulation were higher on the second day than on the first day. Furthermore, in two patients (nos 1 and 2), the values for PCA on the third day after initiation of anticoagulation were higher than those determined on the second day.

The degrees of fit for the regression line for log PCA vs. t are shown in Table 4. An excellent fit was observed for each of the data sets from four of the patients (nos 3, 4, 5 and 6), whereas the data from the remaining three (nos 1, 2 and 7) only showed a moderate fit.

The kinetic parameters for elimination of PCA during the beginning of anticoagulation therapy are presented in Table 4. The mean elimination rate constant of PCA was 0·377 day^{-1} (range 0·242–0·588 day^{-1}). The coefficient of variation in elimination rate constant of PCA was about 28%, demonstrating the considerable inter-individual differences in response to warfarin. The mean plasma half-life of PCA was 1·96 days, suggesting that a 50% PCA reduction would not be observed until about 2 days after initiation of anticoagulation therapy.

The cumulative warfarin dose for each patient was calculated by dividing the sum of the three initial daily doses of warfarin by body weight (Table 2).

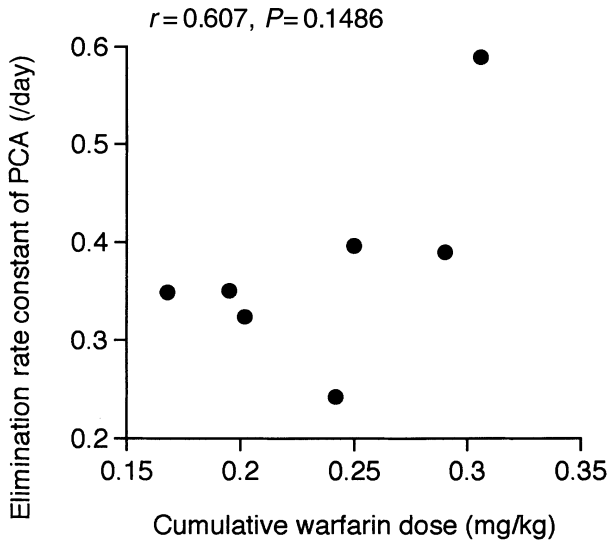

Fig. 1. Relationship between elimination rate constant of PCA and cumulative warfarin dose per kg of body weight. PCA: prothrombin complex activity. Cumulative warfarin dose was calculated by dividing the sum of the three initial daily doses by body weight.

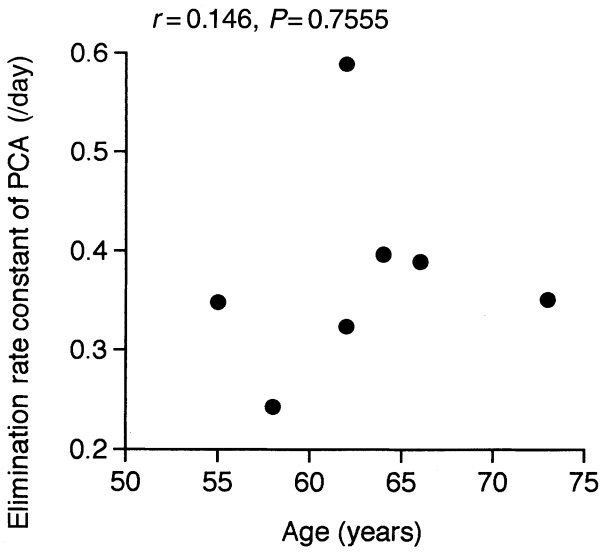

Fig. 2. Relationship between elimination rate constant of PCA and age. PCA: prothrombin complex activity.

The cumulative warfarin dose per kg of body weight ranged from 0·168 to 0·306 mg/kg (mean 0·236 mg/kg). Figure 1 shows that there was no significant relationship between the PCA elimination rate constant and the cumulative warfarin doses during the initiation of anticoagulation therapy ($r = 0{\cdot}607$, $P = 0{\cdot}1486$). The absence of any significant relationship between elimination rate constant of PCA and age is shown in Fig. 2 ($r = 0{\cdot}146$, $P = 0{\cdot}7555$).

DISCUSSION

The present paper describes the time course of changes in PCA for predicting kinetic parameters during initiation of warfarin therapy. The results indicate that the mean plasma half-life of PCA was about 2 days during the initial phases of anticoagulation. However, considerable inter-individual differences were observed in the elimination rate constant of PCA. Furthermore, only two patients were within the target range of PCA by the third day following initiation of therapy. This demonstrates that the PCA response to warfarin is significantly different among patients and, therefore, that a rapid identification of each patient's kinetic parameter is needed to predict the effects of warfarin on PCA in them.

The maximal effect of a single dose of warfarin on PCA develops 36–72 h after the dose is given (4). It appears, therefore, that the effects of a daily dosing of warfarin on PCA are cumulative and are difficult to predict on an intuitive basis. Morrison reported the individual maintenance dose of warfarin on the basis of characteristics of body weight (5). This means that the response to steady-state warfarin after repetitive dosing may be predictable with warfarin doses per kg of body weight. However, our results show that there was no significant relationship between the elimination rate constant of PCA and cumulative warfarin doses per kg of body weight during the initiation of anticoagulation. This suggests that there may be significant differences in PCA kinetics between the initial and steady-state phases of anticoagulation therapy.

Age is a significant determinant of warfarin dosage requirement. O'Malley *et al.* found that warfarin requirements fell with increasing age in patients receiving chronic warfarin therapy (6). The effects of age on PCA kinetics, therefore, are predicted to be significant during anticoagulation with warfarin in a steady-state after repetitive dosing. Our results show that there was no significant relationship between the elimination rate constant of PCA and age during the initiation of anticoagulation therapy. This suggests that, in our patient population, age data may not be useful for predicting PCA kinetics during the initial phases of anticoagulation.

Our results show that, in our patient population, there were no significant relationships between elimination rate constant of PCA and cumulative warfarin doses per kg of body weight or age during initiation of anticoagulation. This suggests that sensitivity to warfarin may be enhanced at different phases of anticoagulation therapy. Furthermore, it appears that age may not be an important predictor of PCA kinetics during initiation of warfarin therapy. Because warfarin is essentially completely absorbed after oral administration (2), pharmacodynamic factors may be more important than pharmacokinetic factors in PCA response to warfarin.

Our results for the PCA response to warfarin are different from those reported by Morrison (5) or O'Malley *et al.* (6). This may be because our patient population is relatively small for determining relationships between PCA kinetic parameters and age or cumulative warfarin doses per kg of body weight. Methods for initiating oral anticoagulation should minimize the time required to achieve steady-state PCA values within the therapeutic range, while protecting the patient from the possibility of overdose and haemorrhage. Our results may be clinically useful for predicting PCA kinetics during initiation of anticoagulation. Research should continue in order to clarify the factors that cause the inter-individual differences in PCA kinetics during warfarin therapy.

REFERENCES

1. Routledge PA, Chapman PH, Davies DM, Rawlins MD. (1979) Factors affecting warfarin requirements: a prospective population study. *European Journal of Clinical Pharmacology*, **15**, 319–322.
2. Holford NHG. (1986) Clinical pharmacokinetics and pharmacodynamics of warfarin: understanding the dose–effect relationship. *Clinical Pharmacokinetics*, **11**, 483–504.
3. Hansten PD, Horn JR, eds. (1995) *Drug Interactions and Updates Quarterly*. Applied Therapeutics, Vancouver, Canada.
4. O'Reilly RA, Aggeler PM, Leong LS. (1963) Studies on the coumarin anticoagulant drugs: the pharmacodynamics of warfarin in man. *Journal of Clinical Investigation*, **42**, 1542–1551.
5. Morrison GW. (1979) Predicting warfarin requirements. *Lancet*, **1**, 167–168.
6. O'Malley K, Stevenson IH, Ward CA, Wood AJJ, Crooks J. (1977) Determinants of anticoagulant control in patients receiving warfarin. *British Journal of Clinical Pharmacology*, **4**, 309–314.