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DETERMINANTS OF ANTICOAGULANT CONTROL IN PATIENTS RECEIVING WARFARIN

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1 A hospital-based drug information system has been used to assess the time for which patients treated with warfarin were outside the range of Thrombotest values 5-10% and 5-15% and to examine possible contributory factors in situations where anticoagulation fell outside these ranges.

2 Anticoagulant control varied with the age of the patient and with concomitant drug therapy but not with patient sex or indication for anticoagulation.

3 Most patients were 'under-anticoagulated' at some stage but patients over 70 years spent significantly longer in the 5-10% range than those in the age range 30-59 years and Thrombotest values of less than 5% were found predominantly in the older group.

4 Patients given drugs known to interact with warfarin spent least time in the defined Thrombotest ranges. Those on drugs known to potentiate warfarin effect had significantly lower Thrombotest values than the other patients studied.

Introduction

Warfarin belongs to a relatively small group of drugs in which the effect of the drug is easily assessed. The therapeutic aim is clearly defined in terms of objective measurement e.g., Thrombotest level between 5 and 15% of normal and a good dose-effect relationship exists. Previous reports have, however, indicated that this ideal is difficult to attain in practice and that, even in specialist centres, desired anticoagulation levels were attained on only about half the occasions (Borchgrevink, Bjerkelund, Abrahamsen, Bay, Borgen, Grande, Helle, Kjorstad, Petersen, Rorvik, Thorsen & Odegaard, 1968; Report of the Working Party on anticoagulant therapy in coronary thrombosis to the Medical Research Council, 1969; Report of an International Review Group, 1970). In an attempt to elucidate some of the contributory factors in situations where optimum anticoagulation was not achieved, the present study has used an epidemiological approach to examine firstly the dose and anticoagulant effect achieved (% time within defined Thrombotest ranges) in a hospitalized population receiving warfarin and secondly the relationship between anticoagulant control and patients' age, sex, pathology and concomitant drug therapy.

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Methods

The hospital-based drug information system has been described by Coull, Crooks, Dingwall-Fordyce, Scott & Weir (1970). All inpatients (240) in the Dundee General Hospitals group who had received warfarin during a 2-year period were identified and their hospital record studied. Data from 177 patients whose case notes contained complete records of warfarin dose, Thrombotest % and details of other drugs taken were analysed. With patients admitted on more than one occasion, only data from the first admission (or first admission for which records were complete) were included in the analysis. The mean daily dose of warfarin was calculated from all warfarin given, excluding 'loading' and 'tailing-off' doses. The Thrombotest % values obtained during the same period (three times weekly) were used to calculate a 'mean Thrombotest %'. In using the Thrombotest data, values above 30 and below 5 were arbitrarily given the values 31 and 4 respectively. Two ranges of anticoagulation were selected (an

Table 1 Anticoagulant control and indication for anticoagulation

	Number of patients	% time outside anticoagulation range 5-10% Thrombotest	5-15% Thrombotest
Myocardial infarction	62	60.0 ± 4.2	27.4 ± 3.8
Atrial fibrillation	14	67.9 ± 7.0	35.8 ± 9.8
Valve prosthesis	7	67.8 ± 15.2	58.2 ± 17.4
Deep venous thrombosis and/or pulmonary embolism	75	59.0 ± 4.0	33.8 ± 3.4
Miscellaneous	14	68.8 ± 8.6	26.5 ± 8.6

Results are given as mean ± s.e. mean

'optimal' Thrombotest range of 5% to 10% and a wider range of 5% to 15%) and anticoagulant effect assessed by determination of the percentage time for which patients were outside these ranges during the period of warfarin therapy.

The indications for anticoagulation in the patients studied were as listed in Table 1. Where there was more than one indication, patients were classified according to the disorder most likely to benefit from anticoagulant therapy.

In studying the influence of concomitant drug therapy on anticoagulant control, the drugs prescribed in addition to warfarin were classified into three groups (see **Appendix**) on the basis of their potential to interact with oral anticoagulants. Drugs were allocated to one or other of these groups according to documented evidence in man (Hansten, 1971) and animal data from the literature:

Group I – known to interact, e.g. barbiturates, phenylbutazone and chloral hydrate.

Group II – may possibly interact, e.g. ethacrynic acid, ascorbic acid, Mandrax (methaqualone/diphenydramine).

Group III – no suspicion of interaction, e.g., penicillin, nitrazepam, practolol. Where drugs from more than one group were prescribed, the therapy was classified as Group I whenever a Group I drug was involved and Group II when Group II and Group III drugs were given.

In the analysis of results, the significance of the difference between means was determined using the Student's *t*-test.

Results

Data from the case records of 177 patients (87 male and 90 female, ranging in age from 30-83 years) were used. During the 2,180 treatment days surveyed, one bleeding episode was recorded. Table 2 summarizes the extent of anticoagulation achieved. Only thirteen patients were continually in the optimal Thrombotest range of 5-10% excluding 'loading' and 'tailing-off' periods. The great majority of patients spent some time with Thrombotest values >15% and were therefore insufficiently anticoagulated. Excessive anticoagulation occurred much less frequently. An analysis of the anticoagulant control overall and for different age groups is given in Table 3, using the two ranges of anticoagulation, 5% to 10% and 5% to 15% Thrombotest. With both anticoagulation ranges there is a clear trend in the change of anticoagulant control with age, the mean values for the 70+ years group being significantly lower than those for the fourth, fifth and sixth decades. Table 3 also shows, however, that the duration of treatment was longer in this group.

In Table 4 a further breakdown of the age-related anticoagulation data is given. This shows quite strikingly that the proportion of patients in whom Thrombotest values <5% were obtained, increases with age and conversely that values >10% were encountered most frequently in younger patients. When the data on mean per cent of the time spent with Thrombotest values < or >10% is considered, it is again apparent that the degree of anticoagulation achieved is greater in old people.

When the sex of patients in the overall study was considered, no significant difference in anticoagulant control was found. The percentage time which male and female patients spent outside the 5% to 10% range was 62.4 ± 3.6 and 59.3 ± 3.5

Table 2 Anticoagulation (Thrombotest %) achieved in the 177 patients studied

Thrombotest range	Number of patients
5-10% for whole treatment period	13
5-15% for whole treatment period	49
<5% at some time	44
>10% at some time	158
>15% at some time	120

respectively and the corresponding values for the 5% to 15% range was 31.6 ± 3.4 and 31.6 ± 3.3.

In Table 1, results are given for the anticoagulant control in patient groups with different indications for anticoagulant therapy. Only the mean value for the valve prosthesis group in the 5-15% range was significantly different from the others. Overall, the results suggest that anticoagulant control does not vary greatly with indication.

Table 5 lists the drugs given in addition to warfarin according to the classification outlined previously. Only three of the 177 patients studied received no additional drugs. The anticoagulant control in patients taking Group II drugs (may possibly interact) and Group III drugs (no evidence of interaction) was similar. Patients on Group I (known to interact) drugs spent 72.5% or 44.5% of the time >10% or >15% respectively, values significantly higher than those occurring in the other two groups ($P < 0.02$).

The number of drugs prescribed in this group was higher than that in patients given only Group II drugs ($P < 0.005$) but was not significantly different from that in patients given Group II drugs. In the 48 patients in Group I, there was no correlation between the number of different drugs given and anticoagulant control.

Anticoagulant dosage

Figure 1 shows the mean daily warfarin dose and anticoagulant control achieved (Thrombotest %) in the 177 subjects studied. The overall trend is for the mean dose to fall, relative to age, after the fifth decade so that in patients aged over 70 years the mean daily dose was 40% lower than in patients aged 40-50 years ($P < 0.001$). The trend with the Thrombotest was similar. There was a significant fall in Thrombotest % in the seventh and eighth decades so that in the eighth decade the Thrombotest value was 34% lower than in the fifth decade ($P < 0.001$) i.e. despite the lower dose of warfarin the anticoagulant effect was greater. The combination of lower dose and more marked anticoagulation indicates a marked increase in sensitivity to warfarin in the aged. There was no difference in the indications for anticoagulant therapy, number of concomitantly administered drugs or patient sex between the groups aged less than 60 years and those older.

The effect of patient's sex on dose and effect of warfarin is shown in Table 6, the mean daily dose in females being 8% lower than for males and the mean Thrombotest value for females 9% lower.

In considering the effect of concomitant drug therapy on warfarin requirement, doses of

Table 3 Anticoagulant control and age

Age of patients (years)	*Number of patients*	*Duration of treatment (days)*	*% Time outside anticoagulation range*	
			5-10% Thrombotest	*5-15% Thrombotest*
30-39	10	11.3 ± 1.8	67.2 ± 9.2	38.7 ± 11.9
40-49	28	10.4 ± 1.0	69.0 ± 5.7	34.3 ± 6.5
50-59	49	11.8 ± 0.9	66.9 ± 4.8	35.3 ± 4.8
60-69	56	13.1 ± 1.0	58.6 ± 4.5	28.9 ± 3.9
70+	34	15.6 ± 1.6	45.8 ± 5.5	27.1 ± 4.5
Overall	177	12.3 ± 1.2	60.8 ± 2.5	31.7 ± 2.4

Results are given as mean ± s.e. mean
The mean Thrombotest values for the 70+ years group are significantly less than the values for the fourth, fifth and sixth decades ($P < 0.005$). The mean duration of treatment was significantly longer in this group ($P < 0.05$).

Table 4 Anticoagulant control and age

Age of patients (years)	*% of patients spending some time in Thrombotest range*		*Mean % time spent in Thrombotest range*	
	<5%	*>10%*	*<5%*	*>10%*
30-39	0	100	–*	70.5
40-49	7.1	97	10.1	65.3
50-59	20.4	92	10.9	72.0
60-69	30.4	86	14.5	62.0
70+	44.1	79	16.0	48.9

* Insufficient data available.

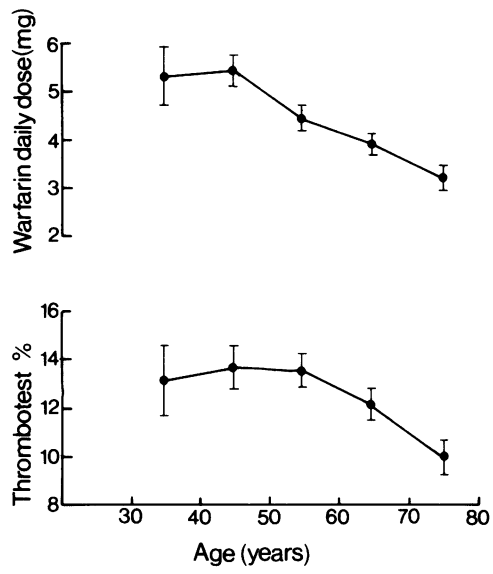

Figure 1 Mean ± s.e. mean daily dose of warfarin given and Thrombotest values for patients in the age ranges shown.

warfarin given to patients on the three different types of additional drugs were not compared since the drugs in Group I and II included both antagonists and potentiators of warfarin effect. The warfarin dose and effect was, however, examined in patients given potentiators or antagonists from the Group I drugs (Table 7). There was no significant difference between the doses given. There was a decreased anticoagulant effect in the group on the antagonist drugs ($P < 0.005$).

Discussion

During oral anticoagulant therapy, the degree of anticoagulation achieved is readily determined using the Thrombotest. In the present investigation, the Thrombotest ranges 5-10% and 5-15% were selected for study.

In carrying out this survey, a hospital-based Drug Information System (Coull *et al.*, 1970) was used to identify patients exposed to warfarin. The retrospective study of these patients' case notes has shown that only 13 of the 177 patients studied had values in the optimal Thrombotest range for the entire period ('tailing-off' and 'loading' dosage period being excluded). Extending the range of Thrombotest values to 5-15% brought 49 of the 177 patients within this range of control for the entire period. At some time 158 out of the 177 had a Thrombotest value greater than 10%.

The time spent by patients outside of the defined Thrombotest ranges is given in Table 3. The overall patient population was found to have

Table 5 Concomitant drug therapy and anticoagulant control

Concomitant drugs	*Mean number of drugs prescribed*	*Number of patients*	*% Time outside anticoagulation range*	
			5-10% Thrombotest	*5-15% Thrombotest*
Group I	7.3 ± 0.6	48	72.5 ± 3.9	44.5 ± 4.5
Group II	6.4 ± 0.4	61	57.9 ± 4.3	28.0 ± 3.6
Group III	4.6 ± 3.4	65	57.4 ± 4.3	27.1 ± 3.4

Results are given as mean ± s.e. mean
The allocation of drugs to Group I, II and III was as described under **Methods** and **Appendix**. The Thrombotest values in the patients on Group I drugs were significantly higher ($P < 0.02$).

Table 6 Warfarin dose and effect in male and female patients

	Patients	
	Males	*Females*
Number of patients	87	90
Mean age (years)	57.4 ± 1.0	58.4 ± 1.2
Warfarin dose (mg)	4.5 ± 0.2	4.2 ± 0.2
Thrombotest %	13.1 ± 0.3	11.7 ± 0.2

Results are given as mean ± s.e. mean

Table 7 Effect of interacting drugs (group I) on warfarin dose and effect

	Group I potentiators	*Group I antagonists*
Number of patients	29	19
Warfarin dose (mg)	4.5 ± 0.3	4.9 ± 0.3
Thrombotest %	11.2 ± 0.8	15.9 ± 1.3

Results are given as mean ± s.e. mean
Allocation of drugs to Group I was as described under **Methods** and **Appendix.**
The Thrombotest values ($P < 0.005$) but not warfarin dose were significantly different.

spent 60.8% of the duration of attempted anticoagulation outside the range 5-10% and 31.7% of the duration outside the range 5-15%. These figures are very similar to those reported from previous retrospective studies (Borchgrevink *et al.*, 1969). In the present study time spent outside the defined ranges varied strikingly with age, the group aged over 70 years spending significantly less time outside these ranges than younger age groups. Thrombotest values of <5% were encountered predominantly in the elderly patients despite the fact that older patients had received smaller doses of warfarin. The results suggest an increased susceptibility of the elderly to the pharmacological effect of this drug.

There are a number of possible explanations for this age-dependent difference in susceptibility to warfarin. With advancing years changes may occur in lean body mass (Forbes & Reina, 1970), in sensitivity to vitamin K or warfarin (Hazel & Baloch, 1970), in serum proteins and in renal function. Alternatively, as occurs with the metabolism of antipyrine and phenylbutazone (O'Malley, Crooks, Duke & Stevenson, 1971), the rate of inactivation of warfarin may decrease in the elderly. A detailed investigation of some of these possibilities is reported elsewhere (Shepherd, Hewick, Moreland & Stevenson, 1977).

When concomitant drug therapy was considered, the simultaneous administration of Group 1 drugs (i.e. known to interfere with the action of warfarin) resulted in a marked increase in the % of time which patients spent outside the defined Thrombotest ranges (Table 7). This reinforces previously expressed views (Koch-Weser & Sellers, 1971a and b) regarding the disadvantages of simultaneous drug therapy when patients are anticoagulated with coumarin agents. The extent of concomitant drug therapy in the present study was surprising – only three out of 177 patients receiving no drugs other than warfarin and 48 of them being given drugs for which there is documented evidence of an interaction in man.

When Group I drugs were subdivided into potentiators and antagonists of warfarin effect (Table 7), Thrombotest values were significantly lower in the patients receiving potentiating drugs thus demonstrating an increased anticoagulant effect. This study has therefore confirmed using an epidemiological approach, the known interaction of some drugs with warfarin.

In conclusion, this study has demonstrated that hospital patients receiving warfarin spend a surprisingly high proportion of time outside the optimal anticoagulation range. Furthermore, age and interaction with other drugs appear to be important determinants.

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Appendix

Drugs given in addition to warfarin

Group I

Potentiators: Anabolic steroids, chloramphenicol, clofibrate, dextrothyroxine, mefenamic acid (Ponstan), methylphenidate, neomycin, phenylbutazone, oxyphenbutazone, phenyramidol, salicylates, disulfiram, quinidine, glucagon, chloral hydrate, phenformin, tricyclic antidepressants.
Antagonists: Griseofulvin, the contraceptive pill, barbiturates, glutethimide, cholestyramine, vitamin K, Welldorm (BCP).

Group II

Paracetamol, laxatives, phenytoin, diazoxide, indomethacin, tetracyclines, thyroid preps., ethacrynic acid, tolbutamide, corticosteroids, haloperidol, antacids, xanthines, mineral oil, carbimazole, ascorbic acid, sulphonamides, Mandrax.

Group III

Meprobamate, chlordiazepoxide, diphenhydramine, thiazide diuretics, nitrazepam, diazepam, penicillin G, narcotic analgesics, reserpine, streptomycin, practolol, phenothiazines, methyl dopa.

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