Br. J. clin. Pharmac. (1977), **4**, 559–565

THE INFLUENCE OF AGE ON THE RESPONSE TO ANTICOAGULANTS

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1 A group of 114 patients on long-term anticoagulant therapy was studied. The daily maintenance dose of both phenprocoumon, bishydroxycoumarin and warfarin was found to be significantly lower in patients aged between 61 and 70 years than in those between 50 and 60 years of age. The mean daily dose of bishydroxycoumarin, however, when expressed on a weight basis, was not significantly lower in the elderly.

2 For bishydroxycoumarin but not for phenprocoumon and warfarin there was found a statistically significant correlation between the daily maintenance dose and the weight of the patient.

3 The mean daily dose of both bishydroxycoumarin and warfarin was 30–40% lower than that recommended in the literature.

4 'Correction' was made for potential drug interference by excluding patients in continuous medication with other drugs known to influence the treatment with orally administered anticoagulants. The interindividual variation in dosage requirements of coumarin drug was thereby reduced in the age groups above 60 years.

5 The level of vitamin-k-dependent coagulation factors, measured by Owren's 'P and P' method (PP%) was significantly lower ($P < 0.001$) in patients of advanced age (between 61 and 70 years) than in younger patients (between 50 and 60 years).

6 The plasma concentration of albumin was significantly lower in patients over 60 years than in those under that age.

7 Correlation ($P < 0.01$) was found between the daily maintenance dose of phenprocoumon and the plasma concentration of albumin.

Introduction

A large number of factors are known to influence the response to orally administered anticoagulants. Excellent reviews on the topic have been published by O'Reilly & Aggeler (1970), Coon & Willis (1970) and Koch-Weser & Sellers (1971a, b). We have recently elucidated certain problems encountered in long-term anticoagulant treatment (Husted & Andreasen, 1976a). From this study it was clear that the risk of bleeding complications is correlated with (1) the level of vitamin-K-dependent coagulation factors during treatment, (2) the coumarin drug used, (3) concomitant drug therapy, and (4) also the age of the patient. A higher risk of bleeding in the elderly was also emphasized by Peyman (1958) and by Coon & Willis (1974). Hayes, Langman & Short (1975a) suggested that a decrease in the plasma albumin concentration in the elderly is a contributory factor since this, at least transiently (Koch-Weser & Sellers, 1971a), enhances the effect of a highly protein-bound drug.

In the present study, an attempt is made to elucidate and explain altered responsiveness in elderly patients.

Methods

The 114 patients in our previous study on long-term anticoagulant therapy (Husted & Andreasen, 1976a) were subjected to further analysis. Table 1 shows a summary of the patient data. All patients who attended the out-patient clinic during a 3-month period were included. Most of them had undergone or were candidates for heart surgery or reconstructive vascular surgery. The physicians from the Departments of Thoracic Surgery and Cardiology, University Hospital, Aarhus, were in charge of the treatment with anticoagulants. The patients were referred to these departments from the entire western part of Denmark, and the anticoagulant drug preferred at the referring hospital was chosen for the therapy.

The prothrombin-complex activity (PP%) was measured by Owren's 'P and P' (prothrombin and proconvertin) technique (Owren & Aas, 1951), and efforts were made to keep the PP% between 10 and 25% of normal activity. The PP% was determined, on the average, every twentieth day, but during stable periods the interval between the determinations was

Table 1 Data of the 114 patients on long-term anticoagulant therapy

Age (years)	
Average	58
Range	30–79
Sex (number of patients)	
Male	67
Female	47
Indication for anticoagulant therapy (number of patients)	
Arteriosclerotic heart disease	14
Rheumatic heart disease	29
Peripheral arterial disease	56
Peripheral venous disease	2
Mixed cases	13
Anticoagulant used (number of patients)	
Phenprocoumon	53
Bishydroxycoumarin	33
Warfarin	28
Duration of treatment (weeks)	
Average	141
Range	4–608

extended up to 2 months and, on the other hand, reduced to 2–4 days, if necessary. The patients were given written information of the PP% value, the recommended dose of coumarin drug and the date of the next control visit.

The information used in this study was obtained directly from the patient by at least two personal interviews at a time interval of more than two weeks, and from the clinical records. All information was transferred to a standard sheet, and notes from the clinical record were checked in the presence of the patient. Careful questioning was made as to current and previous intake of drugs (prescribed as well as others). The albumin concentration in the patient plasma was determined by electrophoresis.

Results

The patients were divided into four groups according to their age at the end of the 3-month investigation period. Figure 1 shows the average individual daily maintenance dose of phenprocoumon, bishydroxycoumarin and warfarin, respectively, for the patients in the four age groups. The 'uncorrected' values on the left side of the vertical bars indicate the daily maintenance dose in each patient. The values on the right side of the vertical bars are 'corrected', i.e. patients receiving drugs which are known from the literature to influence the response to coumarin anticoagulants have been excluded. The drugs concerned are listed in Table 2 (cf. Koch-Weser & Sellers, 1971b; Formiller & Cohon, 1969; O'Reilly & Aggeler, 1970; Husted, Andreasen & Foged, 1976), and the number of cases in which these drugs were given are indicated.

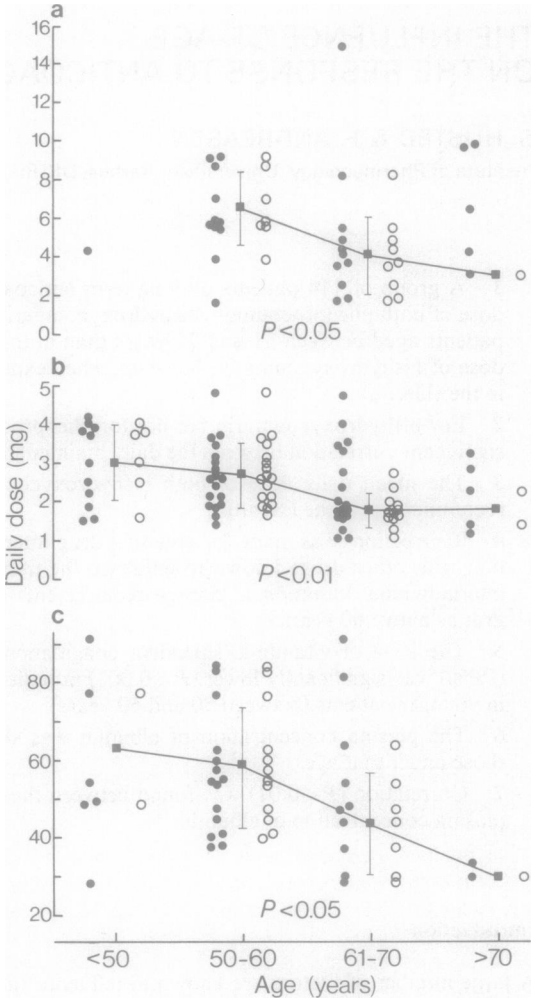

Figure 1 The daily maintenance dose of (a) warfarin, (b) phenprocoumon and (c) bishydroxycoumarin in patients of the four age groups. The vertical bars indicate the mean ± s.d. of data which have been 'corrected' for potential drug interference (○). A significant difference was found between the age group of 50–60 years and that of 61–70 years (values of *P* are indicated). 'Uncorrected' data points (●) are shown on the left side of the vertical bars.

All the drugs encountered were given as continuous co-medication throughout extended parts of the anticoagulation period. The vertical bars in Figure 1 indicate the mean (±s.d.) of individual 'corrected' data in the various age groups.

In Table 3, the average daily maintenance dose (±s.d.) is shown for each of the three coumarin drugs given to patients in the four age groups. The mean daily doses were calculated from the individual 'corrected' and 'uncorrected' values shown in

Table 2 Potentially interacting drugs given as continuous co-medication to the anticoagulated patients

Drugs given	*Number of cases*
Barbiturates	18
Salicylate	4
Meprobamate	4
Chloral hydrate	1
Anabolic steroids	2
Quinidine	4
Allopurinol	1
Thyroid hormones	2
Oestrogens	3
Clofibrate	1
Disulfiram	1
Tolbutamide	4
Morphine	1
Phenytoin	1
Total number of cases	47

Figure 1. The difference between the daily maintenance dose ('corrected' data) for patients aged 50–60 years and 61–70 years was statistically significant both during treatment with phenprocoumon ($P<0.01$), bishydroxycoumarin ($P<0.05$) and warfarin ($P<0.05$). In addition, Figure 1 and Table 3 illustrate that the ingestion of potentially interacting drugs gives rise to more pronounced inter-individual variation in the daily maintenance dose of coumarin drugs.

The mean daily maintenance dose ('corrected' data) of coumarin drug expressed on a weight basis (mg/10 kg of body weight) is shown in Table 4. The difference between patients aged 50–60 years and 61–70 years was statistically significant both for phenprocoumon-treated ($P<0.005$) and warfarin-treated ($P<0.05$) patients, but not for patients receiving bishydroxycoumarin ($0.05<P<0.10$).

For bishydroxycoumarin but not for the other coumarin drugs there was a statistically significant correlation between the daily maintenance dose ('corrected', cf. Table 3) and the weight of the patient (regression coefficient = 0.4798, $P<0.05$).

In Table 5, data are given for both the average duration of the treatment and for the primary disease of the patients in each of the four age groups. There is no distinct difference in the duration of the treatment between the age groups of 50–60 years and 61–70 years. The patients in the age group of 61–70 years had a higher frequency of rheumatic heart failure than those aged 50–60 years. By excluding these patients from the two groups, however, there was still the same statistically significant difference in the dosage levels (cf. Figure 1 and Table 3) for both phenprocoumon and warfarin ($P<0.01$ and $P<0.05$, respectively). Statistical analysis of the remaining data for bishydroxycoumarin could not be performed.

Figure 2 shows the percentual distribution of all the PP%'s determined in patients from the four age groups. Only PP%'s outside the therapeutic range (above 25 or below 10) are illustrated. The hatched columns are 'corrected' for potential drug interference, while the white columns are 'uncorrected'. There is a trend towards a more intensive therapy (more PP%'s below 10 and fewer above 25) of patients aged 61–70 years than in those between 50–60 years. This tendency is, in particular, pronounced for phenprocoumon, which has a high potency and a long biological half life in plasma (Husted & Andreasen, 1976b). Considering the whole patient population, there is a statistically significant difference ($\chi^2=14.75$, $P<0.001$) between the levels of the PP%'s in patients in the age groups 50–60 years and 61–70 years.

Table 3 Mean ± s.d. daily maintenance dose of coumarin drugs (mg) during treatment of 114 patients in long-term anticoagulant therapy. Data 'corrected'—by disregarding data from patients treated with potentially interacting drugs (Table 2)—as well as 'uncorrected' are shown for the four age groups and for all the patients

	Age groups (years)				*All patients*
	<50	*50–60*	*61–70*	*>70*	
	Mean ± s.d. daily maintenance dose (mg)				
Warfarin					
'uncorrected' data	4.28	6.08 ± 2.21	4.95 ± 3.50	6.68 ± 3.08	5.72 ± 2.91
'corrected' data	—	6.57 ± 1.87	4.04 ± 2.02	3.12	4.92 ± 2.25
Phenprocoumon					
'uncorrected' data	2.94 ± 1.04	2.65 ± 0.86	2.28 ± 1.04	2.18 ± 0.87	2.49 ± 1.03
'corrected' data	3.06 ± 0.99	2.72 ± 0.83	1.79 ± 0.43	1.82 ± 0.60	2.43 ± 0.88
Bishydroxycoumarin					
'uncorrected' data	58.02 ± 22.67	55.80 ± 15.49	52.62 ± 21.10	31.55 ± 2.89	53.05 ± 18.84
'corrected' data	62.99 ± 20.40	58.86 ± 15.42	43.56 ± 13.00	29.31	53.02 ± 16.67

Table 4 Mean ± s.d. daily maintenance dose of coumarin drug (mg/10 kg of body weight) during treatment of 114 patients in long-term anticoagulant therapy. 'Corrected' and 'uncorrected' data for the four different age groups are shown as well as the weight of the patients in the age group 'corrected' for drug interference

	Age groups (years)			
	<50	*50–60*	*61–70*	*>70*
	Mean ± s.d. daily maintenance dose of coumarin drug (mg/10 kg body weight)			
Warfarin				
'uncorrected' data	0.73	0.99 ± 0.41	0.73 ± 0.60	0.99 ± 0.43
'corrected' data	—	0.96 ± 0.38	0.57 ± 0.24	0.53
Phenprocoumon				
'uncorrected' data	0.45 ± 0.18	0.43 ± 0.19	0.31 ± 0.13	0.33 ± 0.16
'corrected' data	0.50 ± 0.17	0.44 ± 0.19	0.25 ± 0.05	0.33 ± 0.21
Bishydroxycoumarin				
'uncorrected' data	9.77 ± 5.35	8.28 ± 2.18	7.42 ± 3.18	5.98 ± 0.96
'corrected' data	7.34 ± 2.21	8.45 ± 2.40	6.41 ± 2.75	6.66
Weight of the patients	67.45 ± 10.87	68.09 ± 15.45	71.35 ± 7.72	56.25 ± 14.08

Table 5 The average duration of the treatment and the distribution of the indications for anticoagulant therapy in the patients of the four age groups

	Age groups (years)			
	<50	*50–60*	*61–70*	*>70*
Average duration of treatment (weeks)				
Phenprocoumon	70	76	81	55
Bishydroxycoumarin	138	91	74	36
Warfarin	186	215	194	214
Indication for anticoagulant therapy (%)				
Arteriosclerotic heart disease	11	20	10	25
Rheumatic heart disease	28	16	32	17
Peripheral arterial disease	61	48	45	58
Peripheral venous disease	0	5	0	0
Mixed cases	0	11	13	0

Table 6 The daily requirement of coumarin drug with advancing age in three patients

		Age (years)										
		47	*48*	*49*	*50*	*51*	*52*	*53*	*54*	*55*	*56*	*57*
Daily dose of coumarin drug (mg)	Phenprocoumon	1.60	1.44	1.12	1.13	1.22	1.28	—	—	—	—	—
	Bishydroxy-coumarin	—	—	—	80.3	70.5	70.0	64.5	65.0	64.8	62.2	53.2
	Warfarin	—	—	7.5	7.5	7.5	6.9	6.5	6.3	—	—	—

Figure 3 shows the albumin concentration in plasma of patients under and over 60 years of age. This figure comprises the 37 cases, in which plasma electrophoresis had been performed. None of the patients had congestive heart failure at the time of the albumin determination, and none are postoperative values. Patients aged 61 years or over had a significantly lower plasma albumin concentration than those under that age ($P < 0.01$). The mean levels were 3.8 g% and 2.9 g% in the younger and older groups, respectively.

Figure 4 shows the positive correlation ($P < 0.01$)

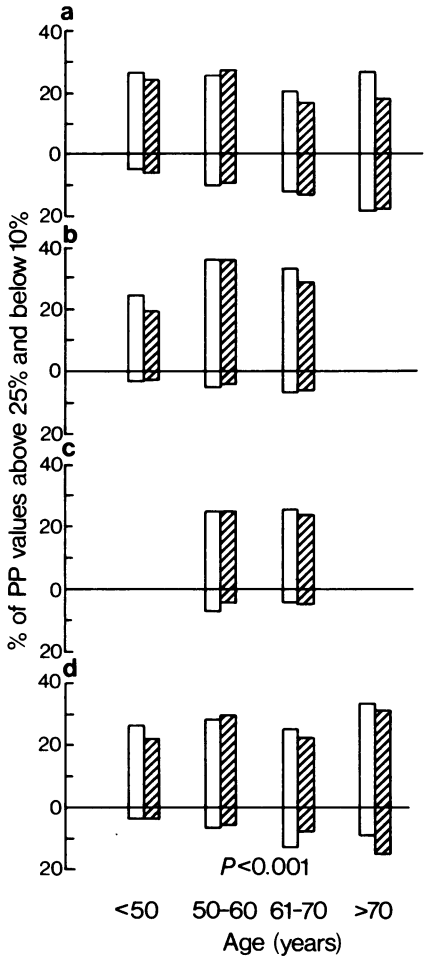

Figure 2 The percentage of PP% values above or below the therapeutic range related to the ages of the patients during anticoagulant treatment with three different coumarin drugs (a) phenprocoumon, (b) bishydroxycoumarin, (c) warfarin and (d) during treatment of the whole patient population. The hatched columns are 'corrected' for data from patients receiving potentially interacting drugs, while the open columns are the 'uncorrected' data. For all the patients the level of the PP% was significantly lower ($P < 0.001$) in the age group of 61–70 years than in the group between 50–60 years.

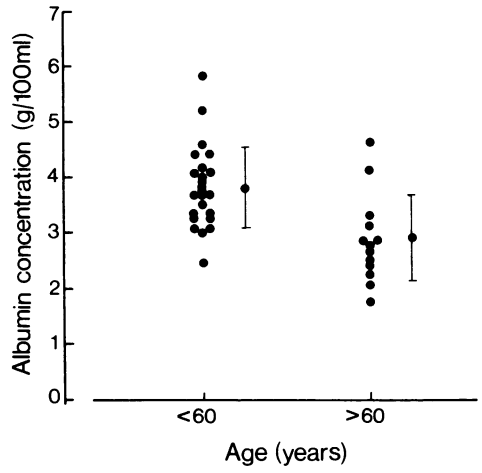

Figure 3 The albumin concentration in the plasma of patients in two age groups. The vertical bars indicate the mean (± s.d.). The difference is statistically significant ($P < 0.01$).

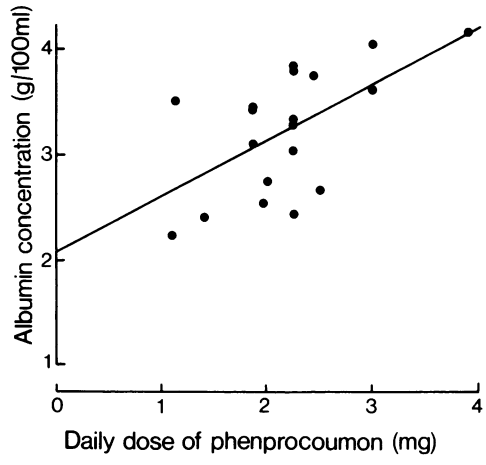

Figure 4. The relation between the daily maintenance dose of phenprocoumon and the plasma concentration of albumin (regression coefficient = 0.597, $P < 0.01$).

between the daily maintenance dose of phenprocoumon and the plasma concentration of albumin in 19 patients who did not receive any potentially interacting drugs (cf. Table 2).

Table 6 shows the variation in daily dosage requirements of the only three patients who had received anticoagulant therapy with either phenprocoumon, bishydroxycoumarin or warfarin for more than 5 years, and who did not start or stop the treatment with any potentially interacting drugs during that period. Over a period of 6–8 years a continuous decrease in the daily maintenance dose of bishydroxycoumarin and warfarin is seen. An initial decrease in phenprocoumon dosage is followed by a slight increase.

Discussion

It has been shown by several workers that age is significantly correlated with the development of bleeding during anticoagulant treatment with

coumarins (Peyman, 1958; Pollard, Hamilton, Christensen & Actor, 1962; Coon & Willis, 1974). In our patients, two-thirds of the bleeding episodes (51 episodes in 34 patients) occurred at an age of 60–69 years although only one-third of the patients were in this age group when the therapy was initiated (Husted & Andreasen, 1976a). In a recent study by Hayes *et al.* (1975a), a decrease in the plasma protein binding of the coumarin drugs in advanced age was suggested to be of some importance in this age-related risk of bleeding.

We found a significantly lower daily maintenance dose of both phenprocoumon, bishydroxycoumarin and warfarin (Figure 1 and Table 3) in patients between 61–70 years than in younger patients (50–60 years). Care was taken to exclude patients receiving drugs which might influence the response to orally administered anticoagulants (Table 2). When this correction was made, a decrease in the interindividual variation in the daily requirements of coumarin drugs was noted (Figure 1 and Table 3). In a reference group of 46 patients, Chriske, Smekal, Knabe & Kray (1973) found a daily maintenance dose of phenprocoumon of 2.75 ± 0.91 mg, as compared with 2.43 ± 0.88 mg ('corrected' data in Table 3) in our 53 patients. The daily maintenance doses found by us of both warfarin and bishydroxycoumarin (Table 3) are lower than those suggested by Nilsson (1973) and Biggs (1976), who recommended a mean daily dose of bishydroxycoumarin of 75 mg (range 25–125 mg) and of warfarin 8–9 mg (range 3–21 mg). The difference between these recommended doses and our findings is marked (Table 3), even when considering the patients in the sixth decade of life, and using the 'corrected' data.

The daily maintenance dose of phenprocoumon and warfarin, when expressed on a weight basis (Table 4) was significantly lower in patients between 61–70 years of age than in the younger patients between an age of 50–60 years. The dose of bishydroxycoumarin, but not of the other coumarin anticoagulants, was positively correlated to the weight of the patient.

This difference between the coumarin anticoagulants has not yet been studied in details, and hence no causal explanation for the observed phenomenon can be given. The pharmacokinetics of bishydroxycoumarin in man are unusual in that drug levels in the plasma decline exponentially following absorption and distribution, but with half-lives which increase with increasing dose (O'Reilly, Aggeler & Leong, 1964). Additionally it has been proposed that the dose dependence in the elimination of bishydroxycoumarin is due to a decrease in the activity of the drug-elimination process and not to distribution effects (Nagashima, Levy & O'Reilly, 1968).

Although the elderly patients received a significantly lower daily maintenance dose of coumarin drug, the level of vitamin-K-dependent coagulation factors in patients of advanced age was significantly lower during treatment. A comparison of the course of the anticoagulant therapy in the patients aged 50–60 years and 61–70 years revealed significantly lower levels ($P < 0.001$) of the PP%'s determined in the elderly patients (Figure 2), as more values were found below 10% of normal activity and fewer above 25%. Patients under treatment with phenprocoumon, show the most pronounced tendency in this respect (cf. Figure 2 and Husted & Andreasen, 1976a).

Phenprocoumon has a long biological half life (Husted & Andreasen, 1976b) and a negligible excretion as unchanged drug (Glogner & Heni, 1973). It might be suggested that reduced rates of elimination of the coumarin drugs are important factors in the reduced requirement and the increased effect of these drugs in advanced age. Prolonged half lives of both phenylbutazone and antipyrine in the elderly have been reported by O'Malley, Crooks, Duke & Stevenson (1971). On the other hand, Hayes, Langman & Short (1975b) found an increase in phenytoin clearance and a decrease in the plasma protein binding of the drug in patients of advanced age.

Both the primary disease of the patient and the duration of the treatment (Table 5) could be ruled out as explanations of the difference observed in the daily requirement of coumarin drug (Table 3). However, the significantly lower concentration of albumin in the plasma of the elderly patients (Figure 3) may offer a partial explanation of the decreased requirement of coumarin drug in these patients. As indicated in Figure 4, there was a positive correlation between the daily maintenance dose of phenprocoumon and the plasma concentration of albumin. Although this supports the assumption that the plasma concentration of albumin is an important determinant in the response to coumarin anticoagulants (Hayes *et al.*, 1975a), other factors must also be considered.

A change in the affinity for coumarin drugs at the 'receptor site' in the liver has been suggested (Husted *et al.*, 1976) as the cause of the increased sensitivity to phenprocoumon during methyltestosteron therapy. This mechanism as well as an increase in the degradation rate of coagulation factors, which was recently observed in patients with acute myocardial infarction (Husted & Andreasen, 1976b), are possible alternative explanations to that of the altered pharmacokinetics suggested above.

Hewick, Moreland, Shepherd & Stevenson (1975) compared the pharmacokinetics and the pharmacodynamics of warfarin in six elderly patients and in four healthy younger volunteers. They found a greater depression of clotting factor synthesis by warfarin in the elderly patients.

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(Received September 27, 1976)