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Effect of age and sex on acenocoumarol requirements

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1 A group of 690 patients (337 males and 353 females) on long-term acenocoumarol therapy was studied.
2 62.8% of the values of the prothrombin ratio were within the chosen therapeutic range (1.8 to 2.7), 21.9% were below 1.8 and 15.3% were above 2.7.
3 The daily maintenance dose, expressed on a weight basis, was found to significantly decrease with increasing age.
4 The daily maintenance dose taken by females was significantly higher than the dose taken by males ($P < 0.05$); the differences between males and females were maximal among patients aged between 21 and 50 years, and disappeared at older ages.
5 Two hundred and twenty-eight haemorrhagic episodes in 160 patients were recorded during a total of 7797 months of follow-up. No lethal haemorrhages were observed. The overall incidence of bleeding episodes among females (3.6%) was higher than among males (2.2%) ($P < 0.001$), even if menorrhagia was excluded ($P < 0.01$).

Keywords acenocoumarol age gender

Introduction

A large number of factors are known to influence the response to orally administered anticoagulants. However, most published data refer to warfarin, and knowledge on the clinical pharmacology of this drug is often applied to other anticoagulants.

Acenocoumarol is the most used oral anticoagulant in Spain and other European countries. The present study was performed to assess the relevance of age and sex as factors determining acenocoumarol dosage requirements.

Methods

Six hundred and ninety ambulatory patients receiving long term treatment with acenocoumarol were included in the study. Table 1 shows the age and sex distribution of these patients. For each patient data were considered after reaching a stable value of the prothrombin ratio. This generally occurred during the first month of treatment. Once a therapeutic effect was achieved (prothrombin ratio of 1.8 to 2.7), patients attended monthly the anticoagulant outpatient clinic of the Hospital de Sant Pau. Their prothrombin ratio was checked in the hospital laboratory using simplastin A and was calculated by dividing the one stage prothrombin time for the patient's plasma by the equivalent time for undiluted control plasma.

Patients' weight and the indications for anticoagulant therapy were also recorded. Table 2 summarizes the distribution of patients according to the diagnoses that apparently motivated the prescription of acenocoumarol by doctors in different departments of the hospital. Other drugs taken by these patients were also recorded.

Data presented here refer to the prothrombin ratios obtained for all patients at a certain time of the follow-up (March, 1982), and are paired with the corresponding daily dose of acenocoumarol prescribed in the previous month to

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Table 1 Age and sex distribution of patients

Age (years)	*Male*	*Female*	*Total*
< 20	2	4	6
21–30	12	15	27
31–40	37	34	71
41–50	77	94	171
51–60	105	111	216
61–70	90	78	168
> 70	14	17	31
Total	337	353	690
(%)	(48.8)	(51.2)	

each patient. The follow-up period took from 4 to 14 months.

Results

Most of the values of the prothrombin ratio were within the chosen therapeutic range. Four hundred and thirty-three values (62.8%) were between 1.8 and 2.7; 151 (21.9%) were below 1.8 and 106 (15.3%) were above 2.7.

Two hundred and twenty-eight haemorrhagic episodes in 160 patients were recorded during a total of 7797 months of follow-up (see Table 3). This gives an overall incidence of 2.9 bleeding episodes per 100 patients treated per month. No lethal haemorrhages were observed. Some of the reported episodes were minor bleedings, and we only report here moderate (disabling) or severe (provoking hospitalization and/or life-threatening) episodes, as identified by interviewing and examining the affected patients. Table 4 shows the distribution of patients with bleeding episodes according to age, sex, and prothrombin ratio recorded at the next monthly follow-up visit.

The results of Table 4 show statistically significant differences ($\chi^2 \leq 15.9$; $P < 0.02$) in the incidence of bleeding episodes between age groups, the incidence being the highest in the 41–50 year decade. The overall incidence of bleeding episodes among females (3.6%) is higher than among males (2.2%) ($\chi^2 = 14.5$; $P < 0.001$). If menorrhagia (15 cases) is excluded, there is still a sex difference ($\chi^2 = 8.5$; $P < 0.01$). On the other hand, no differences in the incidence of bleeding episodes related to the prothrombin ratio have been found. Table 5 lists the mean doses taken by patients who showed a prothrombin ratio between 1.8 and 2.7, according to their age and sex. The overall mean dose taken by females is significantly higher than the dose taken by males ($P < 0.05$), but, as Table 5 shows, the differences between males and females are higher in the first age groups.

As statistically significant differences in weight between males and females have been found for all age decades ($P < 0.01$) except for patients more than 70 years old, we have further explored the possible influence of age and weight on acenocoumarol daily dose, expressed in mg (and not in mg/kg), by means of multiple regression analysis. The F value for age *vs* acenocoumarol daily dose was $F = 31.1$ ($P < 0.00001$); when the pair weight *vs* daily dose was examined, $F = 25.6$ ($P < 0.00001$), suggesting that age and weight have some influence on acenocoumarol daily requirements.

Discussion

Our results suggest the existence of an age-related difference in acenocoumarol requirements between chronically treated patients. Acenocoumarol daily dose expressed in mg/kg fell with increasing age, this decrease being most pronounced from the third to the fifth decade (see Table 5). Variations in the degree

Table 2 Distribution of patients according diagnoses that apparently motivated acenocoumarol prescription

	Males (n)	*Females* (n)	*% of total number of patients*
Heart valvular disease with prothesis	114	119	33.8
Heart valvular disease without prothesis	26	85	16.1
Pulmonary thromboembolism	21	27	7.0
Other thromboembolic diseases	64	46	15.9
Cerebrovascular accidents	14	5	2.7
Atherosclerosis and other ischaemic conditions	16	0	2.3
Ischaemic heart disease	48	3	7.4
Combinations of two or more	22	56	11.3
Unknown	12	12	3.5
Totals	337	353	100.0

Table 3 Episodes of bleeding in 160 patients during a total of 7797 monthly courses of anticoagulant treatment

	First episode	*Second episode**	*Third episode**	*Total*
Gingivorrhagia	40	15	8	63
Subcutaneous haematoma	29	6	2	37
Epistaxis	25	11	0	36
Haematuria	18	7	1	26
Ecchymoses, purpura, petechiae	21	3	1	25
Eye complications	14	5	1	20
Menorrhagia	9	6	0	15
Gastrointestinal bleeding	4	1	1	6
Total	160	54	14	228

* Suffered by the same patient during another month of treatment

of anticoagulation with varying age were not observed. Other studies have found age-related differences in oral anticoagulant requirements. In a multiple regression analysis performed on the data of eighty hospital inpatients who had been given warfarin in the preceding 17 days, Eccles (1975) found that age was the most important predictor of dose that he measured. However, only patients aged 65 to 90 years were included in this study. Studying the warfarin requirements of 177 hospital inpatients, O'Malley *et al.* (1977) found that warfarin requirements decreased with the increasing age from approximately the fifth decade onward, despite an increased degree of anticoagulation in the elderly. However, these studies were confined to hospital inpatients, and they were of short duration.

In a study including 228 ambulatory patients receiving treatment with warfarin for a period not shorter than 6 weeks, Routledge *et al.* (1979) noticed a progressive decline with increasing age from the third decade onwards in the dose required to produce an equivalent degree of anticoagulant control. In this study the dose of warfarin was not given on a weight basis. Although the authors pointed out that weight was also related to warfarin requirements expressed in mg, they did not present data on the relationship of age and sex with the dose of warfarin expressed on a weight basis.

Husted & Andreasen (1977) found that the daily maintenance dose of both phenprocoumon, bishydroxycoumarin and warfarin in 114 patients on long-term anticoagulant therapy was significantly lower in patients aged between 61 and 70 years than in those between 50 and 60 years. However, when expressed on a weight

Table 4 Distribution of patients with bleeding episodes, according to age, sex and prothrombin ratio recorded at the next monthly follow-up visit

	Male				*Female*				
	Prothrombin ratio				*Prothrombin ratio*				
Age (years)	*<1.8*	*1.8–2.7*	*>2.7*	*Subtotal*	*<1.8*	*1.8–2.7*	*>2.7*	*Subtotal*	*Total*
≤ 20	–	–	–	–	–	–	–	–	–
21–30	1	4	5	9	–	4	–	4	13
31–40	1	6	1	8	1	10	2	13	21
41–50	6	18	2	26	15	32	3	50	76
51–60	10	14	1	25	10	28	12	50	75
61–70	5	9	1	15	7	15	4	26	41
> 70	–	–	–	–	2	–	–	2	2
Totals	23	51	9	83	35	89	21	145	228
Total number of monthly courses of anticoagulant treatment	847	2407	554	3808	859	2486	644	3989	7797
Incidence of bleeding episodes (%)	2.7	2.1	1.6	2.2	4.1	3.6	3.3	3.6	2.9

Table 5 Doses of acenocoumarol (mean ± s.e. mean) according to age and sex of patients when the prothrombin ratio was between 1.8 and 2.7 (patients aged 0–20 years were excluded because of low numbers)

	*Males**		*Females***		*Total*	
Age-decade (years)	*Number of patients*	*Dose (mg kg^{-1} day^{-1})*	*Number of patients*	*Dose (mg kg^{-1} day^{-1})*	*Number of patients*	*Dose (mg kg^{-1} day^{-1})*
21–30	6	0.047 ± 0.007	13	0.067 ± 0.006	19	0.060 ± 0.006
31–40	27	0.050 ± 0.004	19	0.055 ± 0.006	46	0.052 ± 0.005
41–50	44	0.049 ± 0.003	58	0.055 ± 0.003	102	0.052 ± 0.003
51–60	75	0.045 ± 0.002	72	0.048 ± 0.002	147	0.046 ± 0.002
61–70	53	0.042 ± 0.003	49	0.043 ± 0.002	102	0.042 ± 0.002
⩾ 71	9	0.041 ± 0.006	8	0.037 ± 0.006	17	0.039 ± 0.006
Totals	214	0.046 – 0.001	219	0.051 – 0.002	433	0.049 – 0.001

* Mean age was 53.7 ± 0.8 years, mean weight was 69.9 ± 0.7 kg.
** Mean age was 52.6 ± 0.8 years, mean weight was 59.2 ± 0.6 kg.

basis, the mean daily dose of bishydroxycoumarin was not significantly lower in the elderly.

The cause of the age-related sensitivity to oral anticoagulants is unclear. A study by Shepherd *et al.* (1977) found no significant differences in the plasma clearance of warfarin after a single oral dose of 1.5 mg/kg between 13 young adults aged 20–40 years (mean 25 years) and 13 others aged 65–94 years (mean 82 years). No other appreciable differences in warfarin pharmacokinetics (plasma half-life, apparent volume of distribution, plasma protein binding or plasma warfarin alcohol levels) were found in the two age groups. However, the results of this study suggested that the increased effect of warfarin in the elderly seems to result from an increased intrinsic sensitivity to warfarin, as there was a greater depression of clotting factor synthesis at equiva-lent plasma warfarin concentrations in six patients aged over 62 years as compared to six patients aged less than 37 years. In addition, the study by Husted & Andreasen (1977) showed that the level of vitamin K-dependent coagula-tion factors was significantly lower in patients of advanced age (61 to 70 years) than in younger patients (50 to 60 years).

We found a significantly higher daily maintenance dose of acenocoumarol in female patients than in male patients (see Table 5). This difference was maximal among patients aged between 21 and 50 years, and disappeared at older ages. Similar studies by other authors, in which patients treated with warfarin were similarly followed up, have not detected such differences. Hewick *et al.* (1975) studied the kinetics of warfarin in 26 patients, and while they found a highly significant difference between young and old participants in the synthesis rate of clotting factors at equal plasma concentrations of warfarin, they did not mention any difference between males and females. In a series of 114 patients treated with phenprocoumon, bishydroxycoumarin, and warfarin, Husted & Andreasen (1977) did not find any difference of sensitivity to oral anticoagulants between males and females. In this series of 114 patients followed during 141 weeks, Husted & Andreasen (1976) recorded 19 bleeding episodes among 47 women and 13 among 67 men, the proportion of thromboembolic manifestations being similar in men and women (14/67 and 10/47 respectively). However, only patients from 50 to 70 years old were included in this study. O'Malley *et al.* (1977) studied the effect of age and sex, among other factors, on the anticoagulant control in patients chronically treated with warfarin. They found an effect of patient's sex on the dose of warfarin and on the prothrombin time, the mean daily dose in females being 8% lower than for males, and the mean Thrombotest value in females being 9% lower than for males.

In a series of 228 ambulatory patients receiving treatment with warfarin, Routledge *et al.* (1979) found no significant difference in the anticoagulant requirements of males and females. However, in five of the six age groups of this study the mean warfarin requirement of males was higher than that of females. The authors suggest that this possibly reflects the slight influence of weight on anticoagulant requirements, since at all ages males were significantly heavier than females. Nonetheless, they did not present the data on the dose of warfarin on a weight basis. The proportion of males and females was not indicated in this paper, and hence the age distribution of patients of each sex cannot be known.

In our study we have found a significant

difference in the acenocoumarol requirements (expressed on a weight basis) of males and females, which is maximal between 21 and 50 years and disappears in older ages. The identification of these sex differences in acenocoumarol requirements may be explained because our series includes a relatively high proportion of patients less than 50 years old, and because the dose of acenocoumarol is expressed on a weight basis.

It is well established that oestrogens contained in oral contraceptives induce some acceleration of the clotting of the procoagulants in the extrinsic and intrinsic clotting systems, as well as a reduction of antithrombin-III levels. There is also evidence of increased fibrinogen levels, depression of fibrinolytic activator activity and associated changes of antiproteases (Poller, 1978). A study of oestrogens given alone for menopausal symptoms performed on a double-blind crossover basis showed a significant shortening of the prothrombin time and an acceleration of the clotting of factors VII and X in the oestrogen-treated group at the three-month stage (Coope *et al.*, 1975). Furthermore, oestrogens when used for the treatment of carcinoma of the prostate carry a well-recognized thromboembolic risk. As these results refer to the effects of exogenous oestrogens, it seems interesting to refer to a more recent study by Kim *et al.* (1981) in which human menopausal gonadotropins were administered over 1 to 2 weeks to seven anovulatory women. The plasma levels of 17 β-oestradiol increased fivefold over the pretreatment value, and this was associated to an increase of fibrinogen level and a decrease of antithrombin III levels. The authors conclude that 'patients on a regimen of human menopausal gonadotropins for induction of ovulation serve as excellent models for the study of 'natural' oestrogen-mediated coagulation parameters'. These data suggest that endogenous oestrogens may also exert an influence on the clotting systems and on antithrombin III activity, and that this might explain the age-related differences that have been found in our study.

With respect to haemorrhagic complications, Pollard *et al.* (1962) observed that the majority of bleeding episodes occurred while the patients' prothrombin times were within the desired therapeutic range. Of all the bleeding episodes observed by Husted & Andreasen (1976), 31.3% occurred while the prothrombin time was below 10% of normal activity. Only 13% of the 228 bleeding episodes recorded in our study occurred while the prothrombin ratio was above 2.7. However, although the value of the prothrombin ratio recorded in our study was obtained during the next visit of the patient to the hospital, it must be taken into account that it is always difficult to obtain a reliable estimate of the time elapsed between the bleeding episode and the discontinuation of treatment, and between the bleeding episode and the visit to the hospital. This could explain the fact that no significant differences have been found in the incidence of bleeding episodes according to the prothrombin time.

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