COMPARISON OF A NEW MICROCRYSTALLINE DICOUMAROL PREPARATION WITH WARFARIN UNDER ROUTINE TREATMENT CONDITIONS

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1 To determine whether two different oral anticoagulants show difference under routine clinical conditions, 71 patients were randomized to treatment with Apekumarol®, a microcrystalline dicoumarol preparation, and 72 patients to treatment with warfarin.

2 During the inpatient phase of treatment both drug groups remained for about 94% of their treatment time within prothrombin value limits of 5–25% (Simplastin A). No statistically significant difference was found between the drugs.

3 While under outpatient care, both drug groups remained for about 80% of their treatment time within prothrombin value limits of 5–25%. No statistically significant difference was found between the drugs.

4 The intensity of control and number of prothrombin-determinations did not differ significantly between the groups.

5 Variations in the daily dose did not differ significantly between the groups.

6 The mean daily dose could not be correlated to mean body weight.

7 The mean daily dose decreased with age for the male patients taking warfarin, not for the female patients. There was no such decrease for either male or female patients taking Apekumarol®.

An additional 137 patients who at the time of the trial were under routine treatment with warfarin were also studied with regard to mean daily dose, age and sex. In this additional group the mean daily dose could be correlated with age in both males and females.

8 No difference between Apekumarol® and warfarin could be demonstrated when tested under routine clinical conditions according to the design of the present study. Sensitivity for warfarin, but not for Apekumarol®, seems to increase with age, this sensitivity has been demonstrated in both sexes.

Introduction

Dicoumarol and warfarin are the two most frequently used oral anticoagulants in Sweden. Both drugs have certain disadvantages: The absorption of dicoumarol is often variable and incomplete and its breakdown is dose related, but this is not the case with warfarin (O'Reilly, Aggeler & Leong, 1964). Commercial warfarin, however consists of two racemic forms each having a different breakdown (Breckenridge, Orme, Wesseling, Lewis & Gibbons, 1974). These characteristics give warfarin an advantage over conventional dicoumarol and this has resulted in warfarin being recommended as the more suitable drug for clinical use (Blombäck, Diener, Forsberg, Hallböök, Hedlund, Lockner, Lund & Reizenstein, 1975).

As the absorption characteristics of dicoumarol seem mainly to depend on the pharmaceutical preparation of the drug (Lozinsky, 1960; O'Reilly *et al.*, 1964) an

attempt was made to improve the absorption of dicoumarol by producing the drug in microcrystalline form. This preparation (Apekumarol®, AB Ferrosan, Sweden) was shown to be virtually completely absorbed at a more constant rate (Korsan-Bengtsson, Holm, Kjällstrand & Korsan-Bengtsson, 1978). It has been shown that Apekumarol® is 20% more effective in depressing prothrombin levels than a conventional dicoumarol preparation (Korsan-Bengtsson *et al.*, 1978).

The results of preliminary studies with Apekumarol® in man suggest that part of the earlier limitations of conventional dicoumarol have now been largely overcome with this new microcrystalline dosage form and that the pharmacokinetic differences between Apekumarol® and warfarin may be of lesser clinical importance. We therefore undertook a randomized clinical study of warfarin and

Apekumarol® in order to determine whether patients treated with Apekumarol® spent a longer-time within therapeutic prothrombin limits than patients treated with warfarin.

Methods

A total of 143 consecutive patients attending the Thrombosis Unit of the Huddinge University Hospital in whom the planned duration of oral anticoagulant treatment was three months or longer were randomized to either Apekumarol® or warfarin treatment. According to the principle described by O'Reilly & Aggeler (1968) treatment was started with a fixed dosage for each drug until prothrombin values had become lower than 30% (normal range 35–140%), after which treatment was continued with individualized doses, these being about 50% of the initial dose.

The initial dosage of Apekumarol® was 160 mg/day during the first half of the study but this was increased to 200 mg/day for the remainder. Warfarin was given initially at a dosage 15 mg/day.

In most patients treatment was started with an infusion of intravenous heparin, which was given parallel to the oral anticoagulants until the therapeutic values had been maintained for 2 to 3 days.

Prothrombin levels were determined by the Simplastin A method.

All patients were hospitalized during the initial phase of therapy. During this time daily prothrombin determinations were performed until stable values had been achieved. Thereafter, prothrombin determinations were carried out while in hospital mostly on alternate days. After 1 to 2 weeks of therapy, under hospital conditions, the patients were usually allowed to leave hospital to continue their treatment as outpatients. The frequency of prothrombin determinations under outpatient conditions was determined individually according to the stability and the niveau of prothrombin values. Both drugs were always prescribed by the same physician, but there were several change-overs in the prescribing physician as the study progressed. The aim was to keep the prothrombin values between 10 and 15%, however values between 5 and 25% were considered to be within the therapeutic limits since no major bleeding episodes or re-thromboses were observed within these limits in our study.

Measurements were made of the time it took to achieve therapeutic prothrombin values after institution of the anticoagulant therapy and of the time during which the patients were remained within therapeutic prothrombin limits, both as inpatients and as outpatients. These latter measurements were also related to the total treatment time. Statistical testing was both age and sex-adjusted by means of variance analysis.

The statistical analyses were performed according to Student's *t*-test.

Results and discussion

Seventy-one patients were randomized to Apekumarol® and 72 to warfarin.

Of the 71 patients randomized into the Apekumarol® group, six could not be evaluated; four never started treatment due to incorrect randomization, while two received the wrong drug. Nine further patients were only included in part of the evaluation, seven because of incomplete data, one because of transfer to another hospital and one due to death, the cause of which was unrelated to the anticoagulant treatment.

Of the 72 patients randomized into the warfarin group, 69 were treated. The remaining three patients were incorrectly randomized and never started treatment. Twenty-two further patients who received warfarin were only included in part of the study: In twelve of these patients treatment was stopped for various reasons, but not because of side-effects. In eight patients data were incomplete, and two patients died due to causes unrelated to the anticoagulant treatment.

The mean age of the patients in each group did not differ statistically, not even when the sexes were compared within or between the groups (Table 1).

The patients allotted to the two treatment groups were thus comparable with respect to age and sex. In some of the smaller subgroups a degree of skew in the distribution was observed for which corrections were made when making the statistical calculation by analysis of variance. The means and the standard deviations in the tables are, however, unadjusted.

It took a significantly shorter time to reach therapeutic prothrombin values when warfarin 15 mg/day was given than when Apekumarol® 160 mg/day was given as the initial dosage (Table 2). When the initial dosage of Apekumarol® was increased to 200 mg/day the therapeutic prothrombin values were reached equally fast in both groups (Table 2). This illustrates the point that speed in depressing coagulation factors with different anticoagulants depends to a great extent in providing a sufficient dose (Aggeler & O'Reilly, 1966). It can therefore be stated that 200 mg/day Apekumarol® and 15 mg/day warfarin are in this respect about equivalent doses. However, it should be pointed out that the mean age of patients in these subgroups differed significantly ($P=0.039$). The mean age for the Apekumarol®-subgroup was 64.5 years compared to 57.0 years in the warfarin subgroup and this may possibly have masked a difference between the two drugs.

Initial treatment with the respective anticoagulants was carried out on an inpatient basis for a mean duration of about twelve days. During this 'inpatient'

phase of treatment the patients remained for about 94% of their treatment time within the therapeutic prothrombin limits (Table 3). The total treatment time did not differ statistically between the drugs. There was no statistical difference in the time spent by the respective patient groups within therapeutic prothrombin limits or the percentage time spent within therapeutic limits (Table 3).

After being discharged from hospital inpatient care

the treatment was continued for a mean of about four months as hospital outpatients. During this 'out-patient' phase of treatment the patients remained for about 80% of their treatment time within therapeutic prothrombin limits. There was no statistical difference between the drugs tested (Table 4).

The total time our in- and outpatients spent within therapeutic prothrombin limits was longer than that reported by other investigators (Borchgrevink,

Table 1 Age and sex of patients studied (Mean $\pm$ s.d.)

	<i>All patients</i>	<i>Females</i>	<i>Males</i>
Apekumarol®	59.8 $\pm$ 15.3 <i>n</i> = 65	57.4 $\pm$ 16.1 <i>n</i> = 29	61.7 $\pm$ 14.5 <i>n</i> = 36
Warfarin	58.4 $\pm$ 17.2 <i>n</i> = 69	59.0 $\pm$ 18.2 <i>n</i> = 37	57.8 $\pm$ 16.2 <i>n</i> = 32
Statistical difference	NS	NS	NS
	Apekumarol® Warfarin:	females/males: females/males:	NS NS

Table 2 Time to reach therapeutic prothrombin values (Mean $\pm$ s.d.)

Apekumarol®	160 mg	2.9 $\pm$ 0.7 days	<i>n</i> = 30
Warfarin	15 mg	2.5 $\pm$ 0.7 days	<i>n</i> = 33
<i>(P</i> = 0.013)			
Apekumarol®	200 mg	2.9 $\pm$ 0.7 days	<i>n</i> = 27
Warfarin	15 mg	2.6 $\pm$ 0.6 days	<i>n</i> = 29
NS			

Table 3 Inpatient results (mean $\pm$ s.d.)

	<i>Treatment time (days)</i> <i>(A)</i>	<i>Time within therapeutic limits (days)</i> <i>(B)</i>	<i>B/A</i>
Apekumarol®	12.5 $\pm$ 15.1	10.8 $\pm$ 11.4	0.93 $\pm$ 0.12 <i>n</i> = 63
Warfarin	11.2 $\pm$ 10.6	10.6 $\pm$ 10.4	0.94 $\pm$ 0.12 <i>n</i> = 65
Statistical difference	NS	NS	NS

Table 4 Outpatient results (mean $\pm$ s.d.)

	<i>Treatment time (days) (A)</i>	<i>Time within therapeutic limits (days) (B)</i>	<i>B/A</i>
Apekumarol®	113.5 $\pm$ 63.9	87.4 $\pm$ 55.3	0.76 $\pm$ 0.17 <i>n</i> = 63
Warfarin	131.3 $\pm$ 84.1	102.7 $\pm$ 77.2	0.79 $\pm$ 0.25 <i>n</i> = 53
Statistical difference	NS	NS	NS

Bjerkelund, Abrahamsen, Bay, Borgen, Grande, Helle, Kjorstad, Petersen, Rorvik, Thorsen & Odegaard, 1968; O'Malley, Stevenson, Ward, Wood & Crooks, 1977) but this may, however be explained at least in part, by the wider prothrombin limits set in our study (5–25%) compared with the Thrombotest limits of the authors cited, namely 5–15%.

These findings indicate that under the routine clinical conditions applied in this limited patient material there appears to be no practical differences between the drugs tested: Patients on Apekumarol® and warfarin maintained their therapeutic prothrombin values to the same degree. These findings are in contrast to those reported by Husted & Andreasen (1976), who found warfarin to be superior to bishydroxycoumarin and phenprocoumon in maintaining therapeutic prothrombin values. Their study, however, is limited by the fact that it was retrospective and the results are based on an inhomogeneous group of patients.

There is always the possibility of improving prothrombin value stability in a given treatment group by more frequent controls and adjustments in dosage, especially when under outpatient care. In order to exclude such biasing influences in the present study a comparison was made of the frequency of prothrombin determinations in both groups of outpatients (Mean $\pm$ s.d. number of prothrombin determinations Apekumarol® group 9.1 ± 4.8 , warfarin group 8.6 ± 4.9). There was no statistical difference between the groups. Prothrombin levels were determined about every other week in our outpatients. (During inpatient treatment the prothrombin levels were determined daily or every other day in both groups, thus there was much less risk of such bias during inpatient treatment.)

An analysis of the daily drug treatment data sheets was also carried out to determine whether the daily dose of one drug had to be varied more frequently

than that of the other in order to maintain the prothrombin values at the intended level. For this purpose the mean daily anticoagulant dose for each patient was calculated.

To make the mean daily doses comparable, in order to overcome problems associated with differing amounts of active substances in both preparations, the standard deviation of this mean for each patient was expressed as a percentage, thus providing an indication of the degree of variation in the daily dose. The mean ($\pm$ s.d.) values of this percentage for both groups were compared (40.5 ± 33.2 , $n=65$ for Apekumarol® group; 41.6 ± 34.3 , $n=69$ for warfarin group). The results indicate a wide variation in the mean daily tablet dose for both groups of about 40%. No difference could be found between the treatment groups.

The data were also analysed to see whether a correlation could be found between the mean tablet dose and mean body weight for patients in the respective treatment groups as a whole and for males and females within the groups, separately (Table 5). No correlation could be demonstrated.

Husted & Andreasen (1977) found that a therapeutic dose of bishydroxycoumarin could be correlated to the bodyweight of the patient but that such a correlation could not be found for either phenprocoumon or warfarin.

To determine the influence of age on therapeutic dosage requirements, the mean daily tablet intake of each patient was correlated to the patients age (Table 6). A strong negative correlation was found for the warfarin group. This indicates that with increasing age the patients need significantly lower doses of warfarin to achieve therapeutic prothrombin levels. No such correlation could be found for the Apekumarol® group.

A more detailed analysis of the material revealed a significant correlation between dose and age for the

Table 5 Patients weight and its correlation to mean tablet intake

<i>Apekumarol®</i>	<i>All</i>	<i>Females</i>	<i>Males</i>
<i>n</i>	38	14	24
Correlation coefficient	–0.034	+0.179	–0.113
Statistical significance	NS	NS	NS
<i>Warfarin</i>	<i>All</i>	<i>Females</i>	<i>Males</i>
<i>n</i>	47	27	20
Correlation coefficient	+0.039	+0.267	–0.241
Statistical significance	NS	NS	NS

males taking warfarin but not for the females (Table 6). Patients in the Apekumarol® group did not show any sex correlated variation of the mean dose.

The inability to find a correlation between dose and age for the females in the warfarin group could have been due to the small number of patients in this subgroup ($n=32$). The authors therefore investigated an additional 137 patients who were currently under treatment with warfarin at Huddinge University Hospital. To obtain the mean tablet intake for each patient a mean of 112 tablet ingestions were analyzed (range 28–631). The results of this study are presented in Table 7. It can be seen that a statistically significant negative correlation between mean tablet dose and age was found for the whole group, and for both males and females when analysed separately.

Husted & Andreasen (1977) have reported greater sensitivity for warfarin with increasing age and in addition they also found a connection between age and dose for bishydroxycoumarin. This study was however not controlled and the patient material was inhomogenous. Separate analyses for the different sexes were not performed.

In another retrospective study (O'Malley *et al.*, 1977) found that elderly patients needed significantly

lower warfarin doses than the younger adults. The mean warfarin dose for the females did not differ from that of the males. Correlation between dose and age was however not calculated separately for both sexes.

Several reasons for the connection between age and dose have been proposed: Changes in the lean body mass (Forbes & Reina, 1970), changed sensitivity to vitamin K or warfarin (Hasel & Baloch, 1970), the rate of inactivation of warfarin being possibly decreased with age (O'Malley *et al.*, 1977, Husted & Andreasen, 1977) lower albumin values in the aged, a change of the affinity of the receptor site and an increased degradation rate of coagulation factors (Husted & Andreasen, 1977).

Shepherd, Hewick, Moreland & Stevenson (1977) showed that vitamin K dependent clotting factors were more effectively inhibited by warfarin in the elderly. Clotting factor degradation, however, did not change with age, neither did the pharmacokinetics of warfarin. The authors concluded that the age related changes are caused by an increased sensitivity to warfarin with age.

In summary it can be stated that, no difference between Apekumarol® and warfarin could be demonstrated when tested under routine clinical

Table 6 Mean daily tablet intake correlated to the patients age

	All	Females	Males
Apekumarol®			
<i>n</i>	65	29	36
Correlation coefficient	-0.198	-0.196	-0.126
Statistical significance	$P > 0.05$	$P > 0.05$	$P > 0.05$
Warfarin			
<i>n</i>	69	37	32
Correlation coefficient	-0.365	-0.237	-0.483
Statistical significance	$0.01 > P > 0.001$	$P > 0.05$	$0.01 > P > 0.001$

Table 7 Daily tablet intake correlated to the patients age (mean $\pm$ s.d.) in a separate group of patients currently under treatment with warfarin

	All	Females	Males
<i>n</i>	137	59	78
Correlation coefficient	-0.320	-0.362	-0.338
Statistical significance	$P < 0.001$	$0.01 > P > 0.001$	$0.01 > P > 0.001$
Age (years)		59.1 ± 17.5	58.4 ± 13.5
Statistical difference		NS	
Mean number of tablets/day		2.57 ± 1.16	2.46 ± 1.20
Statistical difference		NS	

conditions according to the design of the present study. Sensitivity for warfarin, but not for Apekumarol®, seems to increase with age and this sensitivity has been demonstrated in both sexes.

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