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The potentiation of acenocoumarol anticoagulant effect by amiodarone

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1 Out of 690 patients (337 males and 353 females) on long-term acenocoumarol therapy, 80 (35 males and 45 females) were taking amiodarone. Forty patients had started amiodarone treatment while being treated with acenocoumarol. Of these, nine patients had begun amiodarone treatment while taking acenocoumarol.

2 The relation between the daily dose of acenocoumarol and the prothrombin ratio (AC dose/PR ratio) has been considered a useful indicator to study the interaction between amiodarone and acenocoumarol.

3 Differences of acenocoumarol daily dose between takers and non-takers of amiodarone were statistically significant ($t = 5.35$; $P < 0.001$) for the whole population, for all the age groups, and also among males ($t = 2.43$; $P < 0.01$) as well as among females ($t = 5.38$; $P < 0.001$).

4 Out of 40 patients chronically treated with acenocoumarol in whom amiodarone was instituted, 32 showed a decrease of the AC dose/PR ratio, while in eight patients no change was recorded (paired t-test, $t = 5.82$; $P < 0.001$).

5 In 15 patients who were being concomitantly treated with acenocoumarol and amiodarone, amiodarone was discontinued. An increase of the AC dose/PR ratio was recorded (paired t-test, $t = 4.01$; $P < 0.001$).

6 Nine patients had started treatment with amiodarone while receiving acenocoumarol and a decrease of the AC dose/PR ratio was documented; amiodarone was discontinued some months later, and an increase of the AC dose/PR ratio was seen.

Keywords acenocoumarol amiodarone anticoagulant effect

Introduction

An interaction between the antiarrhythmic drug amiodarone and other drugs, particularly warfarin (Martinowitz *et al.*, 1981; Hamer *et al.*, 1982) and digoxin (Moysey *et al.*, 1981) has been suggested. However, the observations refer to a limited number of patients, and only in two case reports, one referring to digoxin (Moysey *et al.*, 1981) and another referring to warfarin (Serlin *et al.*, 1981), have plasma concentrations been measured. In this paper we present data on the steady-state plasma concentrations of acenocoumarol related to prothrombin ratio before and after the institution of chronic treatment with amiodarone and before and after its discontinuation.

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Methods

A cohort of 690 ambulatory patients receiving long term treatment with acenocoumarol has been followed up for some years. Once attained a stable value of the prothrombin ratio (PR) (PR of 1.8 to 2.7), patients attended once a month the anticoagulant out patient 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. The daily dose of acenocoumarol was individualized according to the PR value.

Patients' age, sex, weight, and indication for anticoagulant therapy were recorded at the beginning of the chronic treatment. Daily acenocoumarol dose, PR value, other drugs taken simultaneously, and bleeding episodes were recorded monthly for each patient. Follow-up periods have been of 1 to 10 months until the moment of this study. During December 1981 acenocoumarol plasma concentrations were monitored in 525 patients, in the same blood sample which was used to monitor the PR. They were measured with a h.p.l.c. technique (Van Kempen *et al.*, 1978).

Out of the 690 patients, 80 were taking amiodarone in December 1981. For all patients taking amiodarone in December 1981, the history of previous and subsequent (12 months) use of this drug was reviewed. Forty patients had started amiodarone treatment at some time before this monitoring while their acenocoumarol treatment was monitored monthly. Out of the 80 patients taking amiodarone in December 1981, 16 stopped its use at some time during the following year, without stopping acenocoumarol treatment. One of these patients had an apparent resistance to acenocoumarol, and was taking a dose five–six times higher than the mean value, so that he was excluded in view of this analysis. Of the remaining 15 patients, nine had begun amiodarone treatment while taking acenocoumarol, so that data on the effects of the institution and the discontinuation of amiodarone on acenocoumarol dose/effect ratio could be obtained.

The relation between the daily dose of acenocoumarol and the prothrombin ratio (AC dose/PR ratio) has been considered a useful indicator to study the interaction between amiodarone and acenocoumarol.

Results

1. Comparison between takers and non-takers of amiodarone

Eighty patients (35 males and 45 females) were taking amiodarone in December 1981. Table 1 shows the comparison between amiodarone takers and non-takers. Differences of acenocoumarol daily dose between takers and non-takers of amiodarone were statistically significant ($t = 5.35$; $P < 0.001$) for the whole population. Differences of acenocoumarol daily dose according to age have been described (Arboix *et al.*, 1984). Table 1 shows the acenocoumarol daily dose and plasma concentrations recorded among takers and non-takers of amiodarone according to the age. Statistically significant differences of the daily dose of acenocoumarol were recorded for all the age groups, while there were no differences of acenocoumarol plasma concentrations between

Table 1 Acenocoumarol daily dose and plasma concentrations (mean ± s.e. mean) among patients simultaneously taking or not taking amiodarone.

Age group (years)	*Acenocoumarol daily dose (mg kg^{-1})*		*Acenocoumarol plasma concentration (ng ml^{-1})*	
	Not taking amiodarone (n)	*Taking amiodarone* (n)	*Not taking amiodarone* (n)	*Taking amiodarone* (n)
≤ 30	0.066 ± 0.005 (33)	—	85.4 ± 4.7 (23)	
31–40	0.057 ± 0.003* (59)	0.044 ± 0.005* (12)	104.2 ± 11.0** (45)	62.1 ± 10.2** (10)
41–50	0.057 ± 0.002* (149)	0.044 ± 0.006* (22)	97.0 ± 6.9 (111)	99.9 ± 22.3 (17)
51–60	0.047 ± 0.001* (196)	0.032 ± 0.004* (20)	105.0 ± 6.9 (150)	82.3 ± 10.7 (14)
61–70	0.045 ± 0.002* (144)	0.033 ± 0.003* (24)	102.5 ± 10.2 (110)	99.5 ± 19.1 (17)
≥ 71	0.042 ± 0.003* (29)	0.022 ± 0.001* (2)	105.5 ± 22.5 (26)	86.0 ± 20.2 (2)

*$P < 0.001$, **$P < 0.01$

Table 2 Acenocoumarol daily dose and plasma concentrations (mean ± s.e. mean) among patients simultaneously taking or not taking amiodarone.

	Acenocoumarol daily dose (mg kg^{-1})		*Acenocoumarol plasma concentration (ng ml^{-1})*	
	Not taking amiodarone (n)	*Taking amiodarone* (n)	*Not taking amiodarone* (n)	*Taking amiodarone* (n)
Male	0.048 ± 0.001** (302)	0.036 ± 0.004** (35)	96.6 ± 16.2 (220)	99.8 ± 16.2 (29)
Female	0.053 ± 0.001* (308)	0.040 ± 0.002* (45)	105.9 ± 5.8 (245)	78.7 ± 7.7 (31)
Total	0.051 ± 0.001* (610)	0.038 ± 0.002* (80)	101.5 ± 4.0 (465)	89.0 ± 8.6 (60)

*$P < 0.001$, **$P < 0.01$

amiodarone takers and non-takers, except for the third decade group. In another publication, sex-related differences in the daily doses of acenocoumarol needed to reach a prothrombin ratio of 1.8–2.7 have been described (Arboix *et al.*, 1984). This is the reason why in Table 2 the daily dose and the plasma concentration of acenocoumarol have been compared in each sex group. Differences of acenocoumarol daily dose were statistically significant among males (t = 2.43; $P < 0.01$), as well as among females (t = 5.38, $P < 0.001$). On the other hand acenocoumarol plasma concentrations (which were measured in 525 patients in December 1981) did not show statistically significant differences.

2. *Chronically treated acenocoumarol patients in whom amiodarone was instituted*

Among the 690 patients of the cohort of acenocoumarol users, 40 began a treatment with amiodarone while being treated with acenocoumarol. The AC dose/PR ratio in the month prior to the beginning of amiodarone treatment was 1.34 ± 0.08, and decreased to 1.01 ± 0.07 in the first control after the institution of amiodarone (paired t-test, t = 5.82; $P < 0.001$). Of these 40 patients, 32 showed a decrease in the dose/PR ratio while in eight patients no change was recorded (see Figure 1).

3. *Chronically treated acenocoumarol and amiodarone patients in whom amiodarone was discontinued*

Among the 80 patients simultaneously treated with acenocoumarol and amiodarone in December 1981, 16 had amiodarone administration discontinued (one of these patients was excluded, see **Methods**). While treated with both drugs, the AC dose/PR ratio of the remaining 15 patients was 0.99 ± 0.13, this value having increased to 1.33 ± 0.17 (paired t-test, t = 4.01; $P < 0.001$) 3 months after the discontinuation of amiodarone. Eleven of them showed an increase in the AC dose/PR ratio, while four did not show any change. Nine patients showed this increase in the first monthly control after amiodarone discontinuation, and it

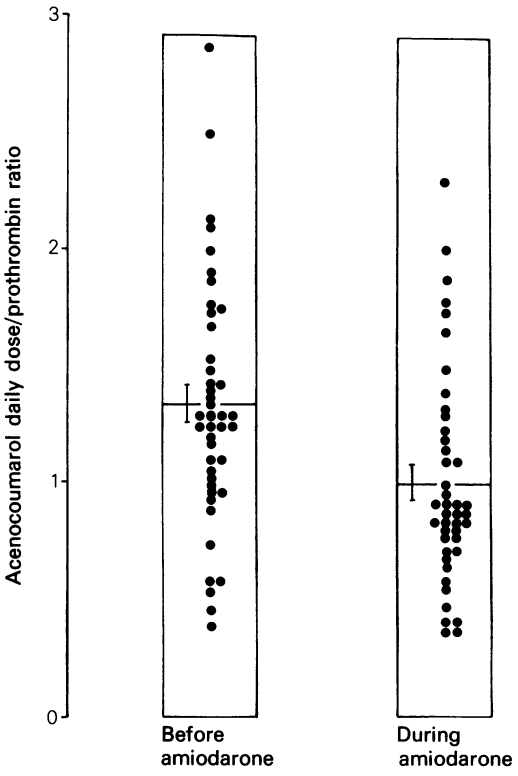

Figure 1 Relationship between the daily dose of acenocoumarol and the prothrombin ratio, in the monthly control prior to and after the institution of amiodarone in 40 patients chronically treated with acenocoumarol.

was still sustained in the second and third monthly control. One patient reached a higher value of the AC dose/PR ratio in the second monthly control, and another patient did not reach a higher value till the third monthly control.

4. Chronically treated acenocoumarol patients in whom the institution and a subsequent discontinuation of amiodarone treatment has been monitored

Nine patients began treatment with amiodarone, while receiving acenocoumarol, but amiodarone was discontinued some months later. Amiodarone treatment lasted 4 months in one, 5 months in a second, and 7 months in a third patient; 8 months in two patients, 9 months in two patients, and 10 months in two patients. In these patients a decrease in the AC dose/PR ratio following amiodarone institution was recorded as well as an increase in the same ratio after amiodarone discontinuation (see Figure 2). The after-treatment increase in the AC dose/PR ratio was seen 1 month after amiodarone discontinuation in six patients, and after 2 months in two other patients. Only one of these nine patients did not present the decrease of the AC dose/PR ratio during amiodarone treatment. She was a 35 year-old woman with a prothestic mitral valve replacement. She was not taking other medications which potentially interfere with oral anticoagulants.

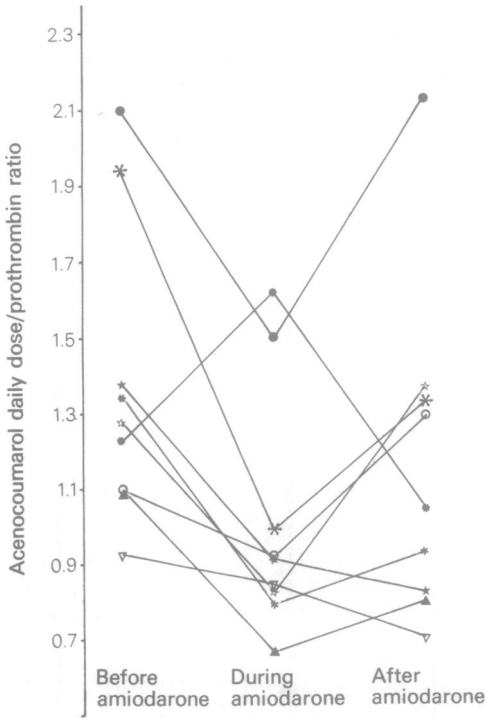

Figure 2 Relationship between the daily dose of acenocoumarol and the prothrombin ratio, in the monthly controls prior to and after the institution of amiodarone, and prior to and after its discontinuation, in nine patients chronically treated with acenocoumarol, to whom amiodarone was given for some months. The figures relating to amiodarone treatment are mean values, amiodarone having been taken for variable lengths of time (4 to 10 months, mean 7.8 months). The figures relating to amiodarone discontinuation are mean values corresponding to the first 3 monthly controls.

Discussion

The study of possible interactions between oral anticoagulants and antiarrhythmic drugs is relevant at least for two reasons. Firstly, these are groups of drugs with a narrow therapeutic range. Secondly, their concomitant administration is very frequent among patients with heart disease.

A number of factors can influence the response to oral anticoagulants. For some of them, for example age, the direction and the degree with which they interfere with the effects of oral anticoagulants has been determined with some precision (O'Malley *et al.*, 1977; Husted & Andreasen, 1977; Shepherd *et al.*, 1977; Routledge *et al.*, 1979). Other factors such as sex and indication for treatment remain controversial and uncertain (O'Malley *et al.*, 1977; Routledge *et al.*, 1979; Arboix *et al.*, 1984). The possible influence of concomitantly administered drugs had already been established in the pioneer paper by O'Malley *et al.* (1977).

Martinowitz *et al.* (1981), Serlin *et al.* (1981), Rees *et al.* (1981) and Hamer *et al.* (1982) have published case reports on a total of 21 patients, suggesting that concomitant administration of amiodarone and warfarin further lowers the levels of vitamin K-dependent coagulation factors. Several mechanisms of interaction have been suggested: (1) a reduction in warfarin metabolism; (2) displacement of warfarin from plasma protein; (3) a reduction in vitamin K absorption; (4) increased vitamin K metabolism; (5) increased metabolism of the vitamin K-dependent coagulation factors; or (6) a direct coumarin-like effect of the drug on vitamin K-dependent factors production.

Our results suggest an interaction between amiodarone and acenocoumarol. When amiodarone is instituted in patients chronically treated with acenocoumarol, the doses of the latter need to be reduced to keep the prothrombin

ratio within the therapeutic range. When amiodarone administration is discontinued in patients receiving the two drugs concomitantly, acenocoumarol doses must be gradually increased to restore the desirable anticoagulation levels. These patients need 1 to 2 months, after amiodarone discontinuation, to achieve a regular dose of acenocoumarol and, as shown in Figure 2, in some of them the pretreatment AC dose/PR ratio is not fully restored. This fact may be related to the prolonged half-life of amiodarone in chronic administration (Kannan *et al.*, 1982; Stäubli *et al.*, 1983).

Mean acenocoumarol daily dose did not show any difference according to age among patients not receiving amiodarone, as well as among the 80 patients receiving the latter drug. For the five age groups, statistically significant differences were found between the two groups of patients (see Table 1). Furthermore, when the differences of the acenocoumarol daily dose were analyzed in both sexes, we found that amiodarone treated patients needed acenocoumarol daily doses lower than those of patients not treated with amiodarone, while in both groups the prothrombin time was within the therapeutic range. These differences were statistically significant (see Table 2).

Acenocoumarol plasma concentrations did not show any difference between patients receiving amiodarone and those not receiving the drug. The stratified analysis of this variable as a function of age and sex did not show any difference either, except for the third age-decade group of patients (this difference being probably due to chance). This suggests a pharmacokinetic interaction, and that pharmacodynamic mechanisms do not play a significant role.

One possible pharmacokinetic mechanism which has been suggested to explain this potentiation of oral anticoagulant effects is displacement of warfarin from plasma proteins (increasing free warfarin levels) (Rees *et al.*, 1981). However, Laoz *et al.* (1984) have shown that although amiodarone is highly bound to plasma proteins (96.3 ± 0.6%), it does not displace warfarin, because these two drugs have different binding sites.

These data support the hypothesis that inhibition of acenocoumarol metabolism by amiodarone could be the mechanism of the observed potentiation. This was also suggested by Serlin *et al.* (1981) when they observed a gradual rise of warfarin plasma concentrations after the institution of amiodarone treatment in one patient.

If it is important to know the mechanism(s) implicated in this interaction, we think that our data stress the need for an accurate monitoring of patients receiving both drugs, by means of a frequent control of prothrombin time and adaptation of the acenocoumarol dose in patients who start or discontinue treatment with amiodarone.

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