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There is no interaction between dipyrone (metamizol) and the anticoagulants, phenprocoumon and ethylbiscoumacetate, in normal caucasian subjects

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Summary

To study possible interactions between anticoagulants and metamizol, as assumed by Mehvar and Jamali (1981), 11 healthy caucasian male subjects were given 1 g of metamizol (dipyrone, Novalgin; Hoechst AG) orally after lowering of the prothrombin ratio by phenprocoumon (Marcumar) in 5 subjects for 7 days and by ethylbiscoumacetate (Tromexan) in 6 subjects for 9 days. Despite hourly measurements of the prothrombin ratio for 8 h after the administration of metamizol no influence on this variable could be detected.

Introduction

The effect on clotting produced by coumarin and indandione derivatives does not result from an action of these drugs in the circulation; rather, it depends on the interference with the normal synthesis of clotting factors by the liver (Levine, 1970).

Interactions between orally administered anticoagulants and many other drugs have often been described and several mechanisms can explain an increase in anticoagulant activity: inhibition of metabolism (phenylbutazone, phenyramidol, chloramphenicol), displacement from plasma protein-binding (phenylbutazone, oxyphenbutazone) or impairment of platelet function (acetylsalicylic acid). The

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potentiation of the anticoagulant activity raises the risk of haemorrhage and this is especially serious in non-hospitalized patients. It is therefore important to establish which other drugs may interfere with oral anticoagulants.

Metamizol (dipyrone) is an analgesic which was first marketed in 1922 and is now in use throughout the world, mainly because of its gastric tolerance and availability for parenteral use. Unlike salicylates and paracetamol, metamizol has never been seen to influence the coagulation process (Standing Advisory Committee for Haematology of the Royal College of Pathologists, 1982) despite an assumption to be found in the literature, based on analogy conclusions (Klotz, 1982) and a study which shows a relatively rapid interaction between dipyrone and ethylbiscoumacetate (Mehvar and Jamali, 1981).

In our study, 11 healthy male volunteers received either phenprocoumon [1] or ethylbiscoumacetate [2]. After reaching a steady-state prothrombin ratio below 50% of normal values, all subjects received single oral doses of 1 g metamizol sodium [3]. Blood samples were taken hourly to determine any effects which metamizol may have on the anticoagulant effect of the two coumarin derivatives.

Materials and Methods

Subjects

All subjects were healthy caucasian male volunteers from the panel of Clinical Pharmacology, Hoechst AG, Frankfurt am Main, who undergo regular clinical and biochemical check-ups. From 12 h before until the end of each trial consumption of the following was prohibited: alcohol, caffeine and nicotine; and the foods: liver, spinach, cabbage, cauliflower and Brussels sprouts. A drug-free period of at least 7 days was observed before the first dose of anticoagulant was given. No drugs other than those under study were administered during the trial. All subjects gave their written informed consent according to the Declaration of Helsinki and Tokyo.

Phenprocoumon was administered to 5 subjects between 38 and 53 years of age (mean 44.6) (Group I). Their weights ranged from 66 to 85 kg (mean 73.2 kg). Ethylbiscoumacetate was given to 6 subjects between 33 and 48 years of age (mean 40.8) (Group II). Their weights were between 67 and 80 kg (mean 76.0 kg).

Dosage regimen

All drugs were administered orally, in tablet form, 1 h before breakfast. The 5 subjects in group I received 12 mg phenprocoumon (4 tablets) on day 1, and from days 2–7 individually adjusted doses, so that a prothrombin ratio below 50% of normal values was reached. In Group II, the 6 subjects were given a loading dose of 900 mg ethylbiscoumacetate (3 tablets) on the first day and from days 2–9 individually adjusted doses.

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[1] Marcumar—Hoffman-LaRoche, F.R.G.

[2] Tromexan—Ciba-Geigy, Switzerland.

[3] Novalgin—Hoechst AG, F.R.G.

All 11 subjects received single doses of 1 g metamizol sodium (2 tablets) simultaneously with the corresponding dose of the anticoagulant, either on day 7 after the beginning of phenprocoumon treatment or day 9 after the beginning of ethylbiscoumacetate treatment.

Blood samples

Two ml of blood were collected by venepuncture in sodium-citrated test tubes at 1 h, 0.5 h and 1 min before drug administration, then every hour up to the 8th hour thereafter. This procedure was followed on day 1 (both groups), day 7 (group I) and days 8 and 9 (group II). A follow-up sample was taken daily (excluding weekends) 1 h before administration of the corresponding anticoagulant dose. Additional samples were taken up to 190 h after the last dose of the anticoagulant. The samples were centrifuged and the plasma immediately separated off.

Measurement of the prothrombin ratio

We applied the Quick method (1957), using thromboplastin extract from human placenta containing calcium ions (0.01 mol/l), Thromborel, Behring Institute, F.R.G. This method was adapted to a coagulometer according to Schnitzger and Ross, Heinricht Amelung GmbH, F.R.G. The determination was performed within 13 min

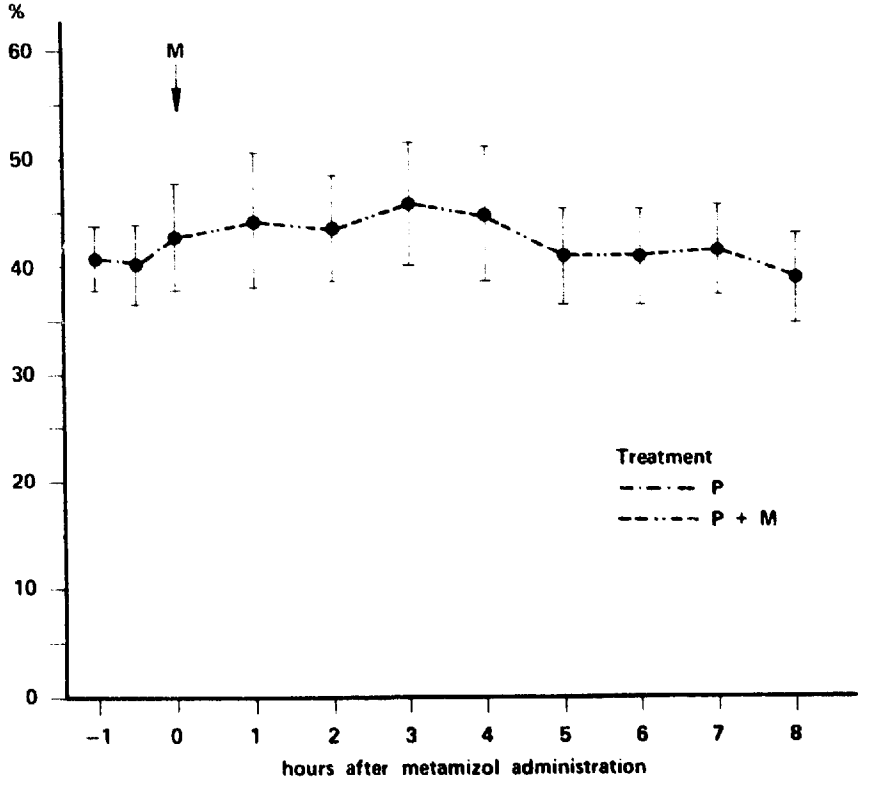

Fig. 1. Course of prothrombin ratio. Metamizol (M); phenprocoumon (P). Mean values and S.E.M. of 5 subjects.

TABLE I
PROTHROMBIN RATIO DURING PHENPROCOUMON METAMIZOL TREATMENT (MEAN VALUES AND S.E.M. OF 5 SUBJECTS)

Treatment	Time	−1 h	−0.5 h	−1 min	+1 h	+2 h	+3 h	+4 h	+5 h	+6 h	+7 h	+8 h	+24 h	+96 h	+120 h	+190 h
					1 g Metamizol p.o.											
Metamizol + phen-	Means (%)	40.8	40.2	42.8	44.4	43.6	46.0	45.0	41.2	41.2	41.8	39.2	39.2	42.4	60.2	90.6
procoumon (Day 7)	S.E.M.	3.0	3.8	5.0	6.3	4.8	5.6	6.2	4.5	4.6	4.1	4.2	4.3	3.9	7.1	5.7

TABLE II
PROTHROMBIN RATIO DURING ETHYLBISCOUMACETATE METAMIZOL TREATMENT (MEAN VALUES AND S.E.M. OF 6 SUBJECTS)

Treatment	Time	−1 h	−0.5 h	−1 min	+1 h	+2 h	+3 h	+4 h	+5 h	+6 h	+7 h	+8 h	+24 h	+96 h	+120 h
					1 g Metamizol p.o.										
Ethylbiscou-	Means (%)	22.8	21.5	22.3	22.3	22.0	20.2	19.0	19.7	18.7	17.7	18.3	–	–	–
macetate (Day 8)	S.E.M.	3.7	3.6	3.6	3.6	3.4	2.7	3.3	2.3	2.2	2.1	2.6	–	–	–
Metamizol + ethylbis-	Means (%)	24.0	21.8	22.0	22.0	21.2	21.7	21.0	20.2	20.0	19.8	20.5	30.7	99.2	99.5
coumacetate (Day 9)	S.E.M.	2.3	2.1	1.7	1.5	1.3	1.6	2.0	1.3	1.6	2.0	1.5	3.8	0.5	0.5

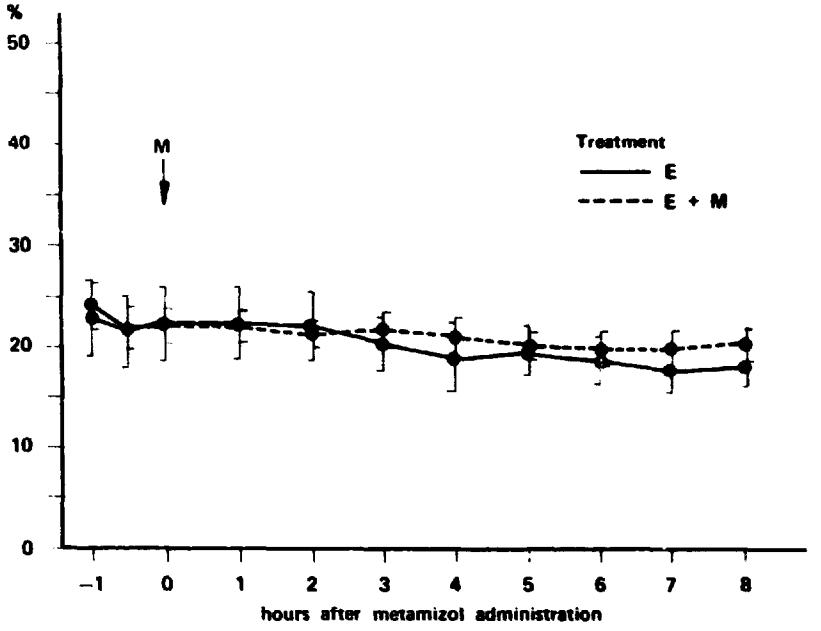

Fig. 2. Course of prothrombin ratio. Metamizol (M); ethylbiscoumacetate (E). Mean values and S.E.M. of 6 subjects.

of blood collection. The results are expressed as percentages of the norm. Each value is the mean of 3 measurements.

Results

Table 1 shows the prothrombin ratio values (means of 5 subjects ±S.E.M.) obtained during phenprocoumon treatment and after administration of phenprocoumon and metamizol. The course of these values is shown in Fig. 1.

The values obtained during ethylbiscoumacetate treatment are shown in Table 2 (day 8, without metamizol and day 9, with metamizol). Fig. 2 shows the course of the prothrombin ratio on day 9 compared to that on day 8.

Discussion

The results obtained during phenprocoumon treatment and after administration of phenprocoumon and metamizol show that a therapeutic oral dose of 1 g of the latter has no influence on the prothrombin ratio during steady-state phenprocoumon treatment.

The same applies for ethylbiscoumacetate treatment, when comparing the prothrombin values before and after oral administration of 1 g metamizol.

On the basis of the structure–activity relationships of metamizol and phenyl-

butazone, Klotz (1982) put forward the theory that metamizol might influence plasma protein-binding of coumarin drugs, as has been described for phenylbutazone (Aggeler, 1967). This might lead to an increase in the anticoagulant effect and a risk of inducing abnormal bleeding. Nevertheless, an interaction of this sort was neither reported in the review article of Breckenridge (1977) in Meyler's Side Effects of Drugs (1980), nor in the recent Clinical Topics of the Standing Advisory Committee for Haematology of the Royal College of Pathologists (1982). The only paper describing a significant potentiation of the anticoagulant activity of ethylbiscoumacetate by metamizol was published by Mehvar and Jamali (1981) who demonstrated a rapid and significantly increased anticoagulation which was maximal 4 h after dipyrone administration and lasted for 7.5 h. None of our findings comply with those in this study. Moreover, no theoretical explanation can be given for this interaction, at least as described by these authors. Although many other drugs have already been shown to displace oral anticoagulants from their plasma protein-binding, it is highly unlikely that coagulation would be reduced to an appreciable degree within only 2 h in this way. Indeed, it is necessary that the vitamin K-dependent clotting factors are sufficiently diminished, since coumarin drugs act on the synthesis of these factors without modifying their degradation. The kinetics of the pharmacological effect is thus dependent on the half-lifes of these clotting factors in the circulation, which are 6, 24, 40 and 60 h for factors VII, IX, X and II, respectively (O'Reilly, 1980). Despite rapid absorption of metamizol (Christ et al., 1973), there is no theoretical explanation for the swift occurrence of the findings reported by Mehvar and Jamali. Another reason for the improbability of these is the fact that metamizol is not as highly bound to proteins as the pyrazolidines (phenylbutazone and oxyphenbutazone) (Hoechst, 1977). Inhibition of the metabolism of ethylbiscoumacetate by metamizol has to be excluded, since this phenomenon is never observed early and it disappears only very slowly. Carter (1965) showed for instance that phenyramidol inhibits metabolism of anticoagulants from the 3rd day onwards and this inhibition was still easily demonstrable up to the 7th day.

Conclusion

In this study, it was demonstrated that the anticoagulant activity of phenprocoumon or ethylbiscoumacetate is not influenced by therapeutic oral doses of metamizol. Anyway, based on current knowledge there is no reasonable explanation for such a conjectured observation.

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