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DIPYRONE–ETHYLBISCOUMACETATE INTERACTION IN MAN

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SUMMARY

Administration of a bolus dose of 600 mg ethyl biscoumacetate and 150 or 300 mg every 12 h thereafter to 7 healthy male volunteers reduced the prothrombin complex activities to 17.01 and 23.87% of the normal activities. In a double-blind study, single oral doses of 1 g dipyrone or placebo were given randomly to two groups of 4 and 3 ethylbiscoumacetate-treated subjects, respectively. As a result of the dipyrone administration, the anticoagulant-induced effect was rapidly and significantly increased. The potentiating effect was maximal 4 h after the dipyrone administration which resulted in 10.23–13.30% of the complex activities and lasted for 7.5 h. It is suggested that the potentiation may be through a mechanism independent of the concentrations of the blood clotting factors.

INTRODUCTION

The effect of coumarin oral anticoagulants on the prothrombin complex activity has been shown to be altered by many drugs (American Pharmaceutical Association, 1976). The alteration takes place at various levels such as absorption, distribution, elimination and interference with receptors.

Dipyrone is an analgesic related to aminopyrine which, despite its side-effect of agranulocytosis (Goodman and Gilman, 1975), is being administered in many countries around the world. The possibility of an interaction between dipyrone and oral anticoagulants has been excluded (Hoechst, 1977) on the grounds that "pyrazolidines (phenylbutazone and oxphenbutazone) reportedly can displace anticoagulants such as coumarin from their binding sites, resulting in severe hemorrhages. Because dipyrone is not as highly bound to proteins as are the pyrazolidines, this type of interaction appears extremely unlikely for the drug." This statement may not be valid because: (1) a given drug may exhibit a limited extent of protein binding but due to its high affinity, replaces another drug which is extensively bound to proteins. For example, in therapeutic doses, salicylates are bound to plasma proteins to a lesser degree than naproxen, but they replace the latter from their binding sites (Segre et al., 1973); and (2) dipyrone may alter

TABLE 1

GENERAL CHARACTERISTICS OF SUBJECTS

Subject	Sex	Weight (kg)	Age (years)
R.M.	M	62	23
V.Z.	M	66	25
S.M.	M	62	24
A.J.	M	70	30
F.G.	M	63	34
S.R.	M	68	25
M.G.	F	55	25
G.A.	M	53	28
S.S.	F	49	22
Mean ± S.D.		61 ± 7	26 ± 4

F, female; M, male.

the oral anticoagulant-induced effect through a mechanism other than replacement from plasma proteins. Therefore, it seemed necessary to investigate the effect of dipyrone on the activity of coumarin anticoagulants in man.

MATERIALS AND METHODS

Subjects

Nine normal Iranian volunteers were randomly divided into two groups (I and II) whose general characteristics are shown in Table 1. Subjects were healthy and had no sign or history of liver dysfunction, renal impairment or gastrointestinal ulcer. They did not take any medication 3 weeks prior to and during the experiment. All subjects were fully informed about the experiment and participated in the project voluntarily.

Dosage regimen

To start the tests, group I received two tablets of 300 mg ethylbiscoumacetate [1] (EBA) as bolus dose and one 300 mg tablet every 12 h thereafter. In the sixth day, 2 h after administration of the first daily dose of EBA, in a randomized double-blind fashion, 4 subjects of group I (tests) received two 500 mg tablets of dipyrone [2] and 3 others took two tablets of lactose as placebo (controls; Table 2).

To group II subjects, who did not receive EBA and had normal prothrombin complex activities, either two 500 mg tablets of dipyrone or two lactose tablets were administered randomly and in double-blind (Table 3).

[1] Geigy, Switzerland.
[2] Hoechst, A.G., Iran.

TABLE 2

ETHYLBISCOUMACETATE- (EBA) INDUCED PROTHROMBIN COMPLEX ACTIVITIES IN SUBJECTS RECEIVING SINGLE ORAL DOSES OF 1 g DIPYRONE (TESTS) OR PLACEBO (CONTROLS) 144 h AFTER COMMENCING EBA TREATMENT

Subjects	Hours after commencing EBA treatment					
	142	144	146	148	150	151.5
Test:						
R.M.	18.10 ± 0.40	18.17 ± 0.81	14.55 ± 1.05 *	13.13 ± 0.56 *	14.83 ± 0.87 *	–
V.Z.	17.90 ± 0.81	17.01 ± 1.02	12.77 ± 0.56 *	10.23 ± 0.18 *	10.74 ± 0.17 *	13.60 ± 0.62 *
A.J.	21.50 ± 0.56	22.38 ± 0.89	15.57 ± 0.56 *	11.83 ± 0.38 *	12.18 ± 0.26 *	19.53 ± 0.83 *
S.M.	23.87 ± 1.23	23.18 ± 1.58	14.30 ± 0.65 *	13.30 ± 0.72 *	14.18 ± 0.91 *	18.20 ± 0.25 *
Controls:						
F.G.	21.86 ± 1.10	18.97 ± 0.51	–	19.10 ± 0.71	20.20 ± 0.93	21.93 ± 0.88
S.R.	19.70 ± 0.37	20.10 ± 0.38	19.54 ± 0.88	21.50 ± 0.56	20.10 ± 0.48	–
M.G.	21.90 ± 0.51	24.24 ± 1.77	23.02 ± 1.10	21.86 ± 1.10	22.50 ± 0.80	–

Values ± standard error of the mean (n = 5) are given; statistical differences were determined using the Student's *t*-test at $P = 0.05$ (after dipyrone and/or placebo treatment against steady-state); *, significant differences.

TABLE 3

QUICK PROTHROMBIN TIME IN SUBJECTS RECEIVING 1 g DIPYRONE (TESTS) OR PLACEBO (CONTROLS)

Subjects	Hours				
	0	2	4	6	7.5
Tests:					
M.G.	11.91 ± 0.66	11.41 ± 0.80	11.41 ± 0.37	10.37 ± 0.21	10.75 ± 0.55
G.A.	11.50 ± 0.44	11.00 ± 0.31	11.12 ± 0.21	11.75 ± 0.55	12.00 ± 0.35
R.M.	11.66 ± 0.40	11.41 ± 0.37	10.58 ± 0.58	11.00 ± 0.57	11.37 ± 0.41
Controls:					
A.J.	12.00 ± 0.31	11.30 ± 0.40	11.50 ± 0.63	10.83 ± 0.25	11.62 ± 0.81
S.S.	10.33 ± 0.47	11.50 ± 0.54	10.25 ± 0.55	10.66 ± 0.68	11.25 ± 0.25

Values ± standard error of the mean are given. Statistical differences was determined using the Student's *t*-test at $P = 0.05$ (no significant differences were observed).

Assay

Samples of 2 ml of blood were collected by venous puncture before the anticoagulant administration and then at intervals of at least every 24 h. Aliquots of 1.8 ml blood samples were added to 0.2 ml solution of 3.8 g/100 ml sodium citrate and centrifuged. Plasma was removed and the prothrombin complex activity was determined using the Quick (1957) method [3]. Prior to EBA administration, the normal prothrombin complex activities were measured against standard plasma [4] in all subjects. Subsequent observed values were converted to per cent normal prothrombin complex activities using citrated test plasma versus normal coagulation control table [5].

Each blood sample was tested at least 5 times and the mean and standard errors were calculated. The statistical differences between samples were determined employing the Student's *t*-test at $P = 0.05$ (Tables 2 and 3).

During steady-state, blood samples were taken at 2, 4 and 6 h after the first daily dose to ensure the consistency of the activities. After dipyrone and/or placebo administration blood samples were taken at 0, 2, 4, 6 and 7.5 h.

RESULTS AND DISCUSSION

Table 2 depicts the mean per cent normal EBA-induced prothrombin complex activities against time at steady-state and after administration of dipyrone and/or placebo to the test and control subjects, respectively. Fig. 1 depicts the observation in one dipyrone-

[3] Thromboplastin liquid (rabbit brain) and 0.02 M calcium chloride of Hyland (Calif., U.S.A.) brand were employed.

[4] Freeze-dried human plasma, Hyland, Calif., U.S.A.

[5] Hyland, Calif., U.S.A.

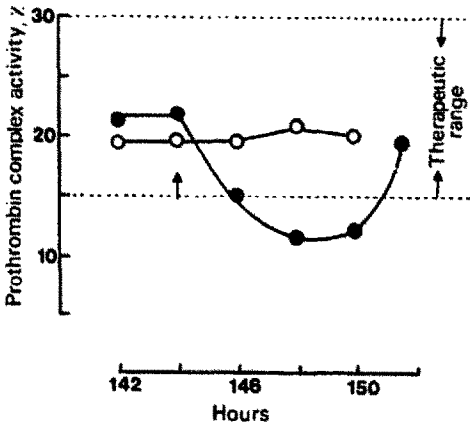

Fig. 1. Prothrombin complex activities in two ethylbiscoumacetate-treated subjects during steady-state and following administration of dipyrone (A.J., •) or placebo (S.R., ○). Arrow at 144 h indicates the time of dipyrone and/or placebo administration.

treated subject compared to a placebo-administered subject. Prior to the administration of the first dose of EBA, all subjects had normal prothrombin complex activities which ranged from 92.27 to 100% of the standard citrated human plasma activity. The steady-state was attained not later than 72 h after commencing the treatment and, except for one subject (S.M.), ranged between 17.01 and 23.87% of the normal activity, which is within the recommended therapeutic range, i.e., 15–30% (Aggeler et al., 1967).

The prothrombin complex activity in subject S.M. was reduced to 13.57% of its normal activity on the third day. Therefore, the daily dose was reduced to half of the initial regimen, i.e. 150 mg every 12 h. As a result, on the fifth day, the effect in this subject reached its new steady-state which was within the therapeutic range (Table 2).

No significant differences were observed between prothrombin activities of the samples during the steady-state in each individual. At steady-state, the response to the treatment in the 6 of the subjects was very consistent, showing a variation of coefficient of 12%. However, as shown in Table 2, after administration of dipyrone, the hypothrombinemic effect of EBA was significantly and to a great extent potentiated. The maximum potentiating effect was observed 4 h and was between 52 and 72% giving rise to 10.23–13.30% of the normal prothrombin complex activity, respectively. The observed values were well below the therapeutic range. The potentiating effect, although diminishing, was significant even after 7.5 h.

On the other hand, in placebo-treated subjects, the EBA-induced prothrombin complex activities remained unchanged and within the therapeutic range.

It is worth emphasizing that the potentiating effect of dipyrone was rapid and seemed to start immediately after the analgesic was absorbed.

The hypothrombinemic action of oral anticoagulants is based on their ability to inhibit the synthesis of certain vitamin K-dependent clotting factors (Nagashima et al., 1969). The onset of action of these drugs is usually between 12 and 24 h (Goodman and Gilman, 1975). This is because, although coumarin anticoagulants may rapidly block the synthesis of prothrombin complex activity, the therapeutic effect does not appear until normal

circulating levels of the complex are significantly reduced. Thus any mechanism which causes a change in either total or protein-free plasma concentration of oral anticoagulants may not elicit its effect in a few hours. Barbiturates (Levy et al., 1970) and rifampin (O'Reilly, 1974) stimulate the metabolism of anticoagulants but their reducing effects appear within days. Phenyramidol inhibits the metabolism of the anticoagulants 3–7 days after administration started (Carter, 1965). Phenylbutazone displaces warfarin from human albumin and significantly potentiates the induced hypothrombinemia (Aggeler et al., 1967). This effect has been detected no sooner than at 24 h. Therefore, the potentiating effect of dipyrone on EBA-induced hypothrombinemia is not likely to result from a change in the absorption, distribution or elimination of the anticoagulant. Alternatively, potentiation through clot-inhibiting reactions, independent of the coagulation factor concentrations, is expected to appear within a short time. Heparin blocks clotting through such a mechanism and its effect, unlike coumarin anticoagulants, is very rapid (Goodman and Gilman, 1975). Heparin is also capable of prolonging one-stage prothrombin time (Moser and Hajjar, 1967). Therefore, if heparin is co-administered with oral anticoagulants, the observed Quick-time will be expected to increase immediately. The observed potentiating effect of dipyrone may also result from a mechanism somewhat similar to that of heparin. However, administration of 1 g dipyrone to subjects with normal prothrombin complex activity did not significantly influence the Quick-time (Table 3). But it should be mentioned that when the normal prothrombin time is 12 sec, a 0.5 sec increase in prothrombin time, which is practically impossible to detect by means of the Quick method, corresponds to a 16% reduction in the complex activity. Therefore, it may be possible that in subjects with normal prothrombin complex activities, dipyrone has prolonged the prothrombin time but the effect is undetectable with the method used in this work. On the other hand, when the prothrombin complex acitivity is reduced to the therapeutic range, a small reduction in the activity will give rise to a prolonged prothrombin time which is easily detectable using the Quick method. This is because the relationship between prothrombine time and the complex activity is a non-linear one. Quinidine (Koch-Weser, 1968) and glucagon (Koch-Weser, 1970) also do not prolong prothrombin time to a clinically significant extent, but both drugs synergistically increase the hypothrombinemic action of warfarin. Therefore, although administration of a single dose of dipyrone may not significantly alter normal prothrombin time, when the prothrombin complex activity has already been reduced to the therapeutic level, the analgesic may further lower the activity, thereby giving rise to hemorrhagic episodes. This is particularly alarming because in spite of its side-effects (Goodman and Gilman, 1975a; Zelenyi, 1970), dipyrone is being administered in many parts of the world as an effective analgesic and antipyretic. This drug is one of the rare non-narcotic analgesics which can be used in injectable form and is sometimes preferred to other analgesics because it does not seem to produce gastrointestinal disturbances. Therefore, since many analgesics are shown to potentiate anticoagulant-induced hypothrombinemia (Sellers and Koch-Weser, 1970; Aggeler et al., 1967; Fausa, 1970; Brodie, 1965) and no report regarding interaction of dipyrone with these agents has appeared, this analgesic may be considered safe and prescribed as an alternative thus increasing the risk of hemorrhage. It should be mentioned that similar to the case reported for heparin (Moser and Hajjar, 1967), a sudden dipyrone-induced prolongation in the prothrombin time may mislead the clinician and

prompt the cessation of the anticoagulant therapy in patients receiving these drugs chronically.

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