Reprinted from THE JOURNAL OF CLINICAL PHARMACOLOGY, February 1996
Vol. 36, No. 2
Lippincott-Raven Publishers Printed in U.S.A.

Enhancement of Anticoagulant Action by Warfarin–Benzbromarone Interaction

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To investigate the interaction between warfarin potassium and benzbromarone, administration of benzbromarone to patients receiving long-term treatment with both drugs was discontinued for 1 week and then resumed, and the resulting changes in the coagulation system were examined. Thrombotest value, activity of coagulation factors II and VIII, concentration of protein induced by vitamin K absence or antagonist-II (PIVKA-II), total plasma concentration of warfarin, and free warfarin concentration were measured during the period of concurrent administration of the two drugs, 1 week after discontinuation of benzbromarone, and after resumption of benzbromarone administration. After administration of benzbromarone had been discontinued for 1 week, the thrombotest value and factor II activity rose significantly whereas PIVKA-II activity dropped significantly compared with corresponding levels before discontinuation, but these parameters tended to revert to the previously maintained levels after resumption of benzbromarone treatment. Activity of the vitamin K-independent factor VIII displayed almost no changes, however. Total plasma warfarin concentration also decreased significantly, and free warfarin concentration was nearly unchanged. These results verified that the anticoagulant action of warfarin is enhanced by concurrent administration of benzbromarone. Accordingly, adequate consideration must be devoted to the prevention of grave hemorrhagic tendencies when these two drugs are administered concurrently.

Warfarin potassium inhibits the biosynthesis of vitamin K-dependent coagulation factors (i.e., factors II, VII, IX, and X) in the liver, thereby manifesting an anticoagulant action, and is widely used for the treatment and prophylaxis of thromboembolism. Warfarin is known to interact with a variety of drugs, notably uricosuric agents, such as sulfinpyrazone,[1] probenecid,[2] bucolome,[3] and allopurinol.[4]

Benzbromarone is a uricosuric agent that has been made commercially available in approximately 20 countries including Japan (launched in 1978), Germany, and France since its use in patients with gout was reported by Delbarre et al.[5] Benzbromarone exhibits a uricosuric effect by blocking tubular resorption of uric acid. Unlike probenecid and sulfinpyrazone, however, benzbromarone does not interfere with the tubular secretion of organic acids, particularly uric acid.[6] Little information is available about interactions of benzbromarone with other drugs, although it is known to react with allopurinol.[7–9]

Warfarin and benzbromarone constitute a pair of drugs with a high probability of concurrent use, particularly in the field of cardiovascular medicine and surgery. Recently, we have encountered phenomena indicating enhancement of warfarin action when administering benzbromarone (Urinorm; Torii Ltd, Tokyo, Japan) to patients undergoing anticoagulant therapy with warfarin. Accordingly, in the present study, the interactions of the two drugs were investigated in further detail in patients receiving concurrent warfarin and benzbromarone.

PATIENTS AND METHODS

Patients

The present study population comprised seven outpatients undergoing concurrent anticoagulant ther-

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TABLE I

Patient Profile

Patient	Sex	Age (yrs)	Status	Warfarin Dosage (mg/day)	Benzbromarone Dosage (mg/day)
1	F	64	Mitral valve replacement (postoperative)	1.25	50
2	M	69	Mitral valve replacement (postoperative)	1.50	50
3	M	62	Mitral valve replacement (postoperative)	1.00	100
4	M	61	CABG (postoperative)	1.75	50
5	F	70	CABG (postoperative)	1.50	50
6	M	68	CABG (postoperative)	2.50	50
7	M	58	Recovery from myocardial infarction	3.00	50

CABG, coronary artery bypass graft.

apy with warfarin and benzbromarone for treatment of gout. Patient data are shown in Table I. The average age (mean ± standard deviation) of the patients was 64.6 ± 4.5 years, and the group included 5 men and 2 women. Three patients had undergone prosthetic valve replacement surgery, three had undergone coronary arterial bypass grafting, and one was recuperating from myocardial infarction; all seven cases were complicated by gout. The mean daily drug dosages were 1.8 ± 0.7 mg of warfarin and 57.1 ± 18.9 mg of benzbromarone. Two patients were given a cardiac glycoside, three were given a diuretic agent, and three were given and a nitrite preparation in addition to concomitant treatment with benzbromarone, but the doses of both warfarin and benzbromarone and the prescription of these concomitant treatments was not changed throughout the study period.

Experimental Procedures

In each case, at a time when the patient was not experiencing an attack of gout, benzbromarone administration was discontinued for 1 week while warfarin administration was continued as usual. Coagulative function was examined at three times: during concurrent administration of the two drugs, after the 1-week discontinuation of benzbromarone, and after resumption of benzbromarone administration. The parameters examined included thrombotest value, factor II (prothrombin) activity, concentration of protein induced by vitamin K absence or antagonist-II (PIVKA-II), and factor VIII activity. In addition, total plasma warfarin and free (not bound to albumin) warfarin concentrations were measured. Because patients visited the clinic on different days, they were not initiated on the study on the same day; there was an entry time lag of 25 days between the first entry into the study and the last.

Analytical Techniques

The analytical techniques employed for measurement of the various parameters were as follows. Thrombotest values were measured by the Owren method,[10] factor II activity by a chromogenic prothrombin time (PT) method,[11] PIVKA-II concentration by enzyme-linked immunosorbent assay (ELISA),[12] and factor VIII by a chromogenic activated partial thromboplastin time (aPTT) method.[11] Total plasma warfarin concentration was assayed by high-performance liquid chromatography (HPLC),[13] and free warfarin concentration was determined by millipore filtration followed by HPLC. Blood sampling after resumption of benzbromarone administration was performed during hospital visits at least 2 weeks subsequent to the day of resumption, at approximately 10:00 AM and before clinical examination.

Statistical Processing

Parameters were measured three times during the study, and the average of the three times was the measured value of each parameter. The paired Wilcoxon test was used for testing the significance of differences among parameters measured during concurrent administration, 1 week after benzbromarone discontinuation, and after resumption of benzbromarone administration. Differences of $P < 0.05$ were regarded as significant.

RESULTS

The average length of time between resumption of benzbromarone administration and subsequent blood sampling was 29.4 ± 6.6 days.

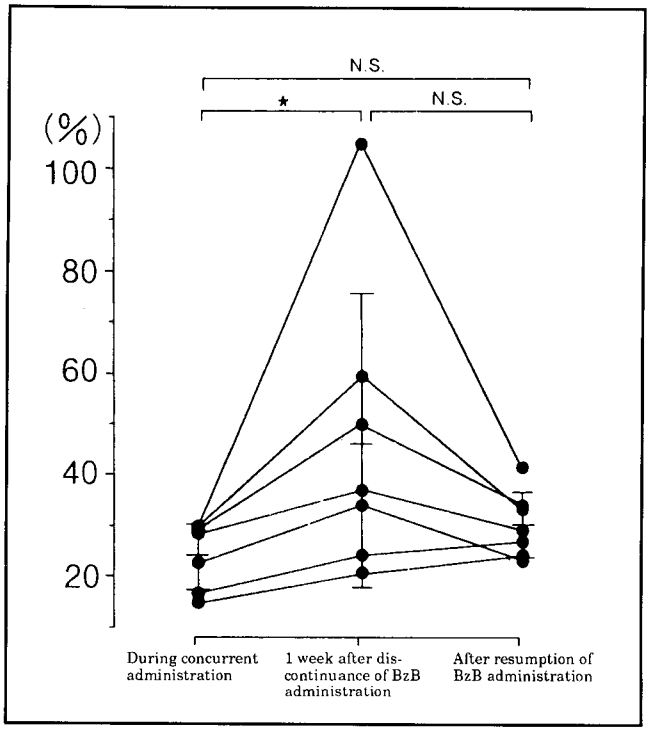

*Figure 1. Changes in thrombotest values after discontinuation of benzbromarone administration in patients concurrently treated with warfarin potassium and benzbromarone: (1) during concurrent administration; (2) 1 week after discontinuation of benzbromarone; and (3) after resumption of benzbromarone administration. Bars indicate mean ± standard deviation; * P < 0.05; NS, not significant by the Wilcoxon test. BZB, benzbromarone.*

Thrombotest Values

The thrombotest constitutes a parameter checked on each day of clinical examination as a central index for assessing the coagulative functions of patients undergoing anticoagulant therapy. Figure 1 shows the changes in thrombotest values concomitant with discontinuation of benzbromarone administration. The values measured during concurrent administration averaged 24.7 ± 6.4%, but after benzbromarone administration had been discontinued for 1 week all patients displayed an increase in this parameter, with values averaging 47.3 ± 28.9% (increase of 91.5%). This difference was significant ($P < 0.05$). After resumption of benzbromarone administration, the levels decreased in five patients and overall values for the group averaged 30.3 ± 6.6%, approaching the level measured during concurrent administration.

Factor II Activity

Coagulation factor II is vitamin K dependent, and its activity is decreased by the action of warfarin. Figure 2 shows the changes in factor II activity concomitant with discontinuation of benzbromarone. The values measured during concurrent administration averaged 63.1 ± 13.0%, but after benzbromarone administration had been discontinued for 1 week all patients displayed an increase in this parameter, with values averaging 79.7 ± 23.9% (increase of 26.3%). This difference was significant ($P < 0.05$). After resumption of benzbromarone administration, these levels decreased in six patients and overall values for the group averaged 66.1±23.1%, approaching the level measured during concurrent administration.

PIVKA-II Concentration

PIVKA-II is a protein induced by vitamin K deficiency or by vitamin K antagonists, such as warfarin. Figure 3 shows the changes in PIVKA-II concentration concomitant with discontinuation of benzbromarone administration. The values measured during

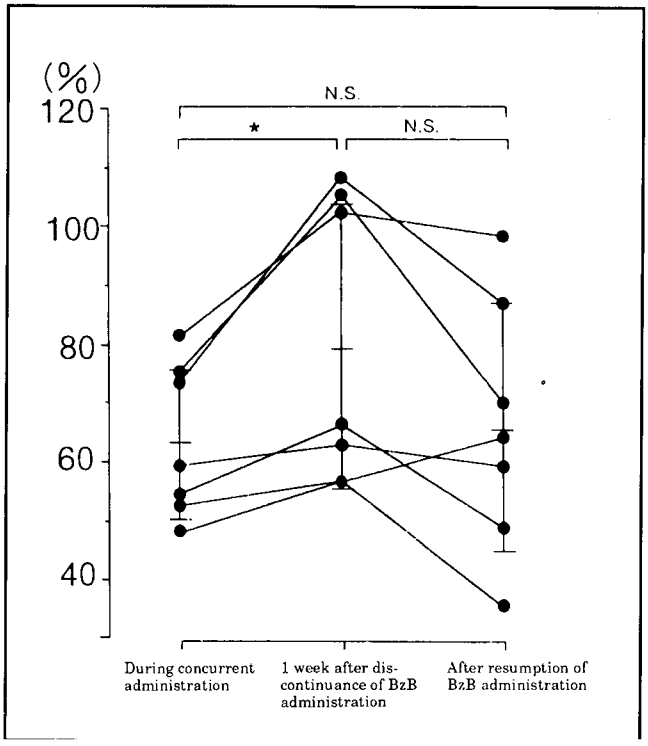

*Figure 2. Changes in activity of coagulation factor II after discontinuation of benzbromarone administration in patients concurrently treated with warfarin potassium and benzbromarone: (1) during concurrent administration; (2) 1 week after discontinuation of benzbromarone; and (3) after resumption of benzbromarone administration. Bars indicate mean ± standard deviation; * P < 0.05; NS, not significant by the Wilcoxon test. BZB, benzbromarone.*

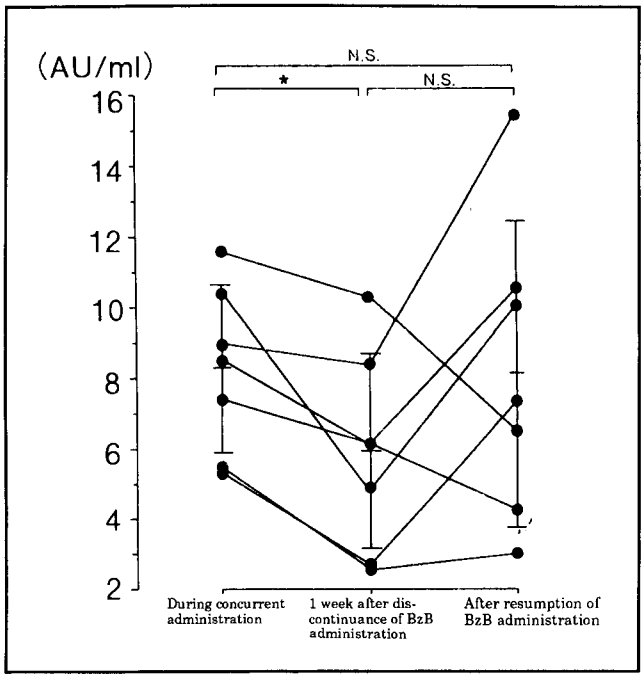

*Figure 3. Changes in PIVKA-II concentration after discontinuation of benzbromarone administration in patients concurrently treated with warfarin potassium and benzbromarone: (1) during concurrent administration; (2) 1 week after discontinuation of benzbromarone; and (3) after resumption of benzbromarone administration. Bars indicate mean ± standard deviation; * P < 0.05; NS, not significant by the Wilcoxon test. BZB, benzbromarone.*

concurrent administration averaged 8.2 ± 2.4 AU/mL, but after benzbromarone administration had been discontinued for 1 week all patients showed a decrease in this parameter, with values averaging 5.8 ± 2.8 AU/mL (29.7% decrease). This difference was significant ($P < 0.05$). After resumption of benzbromarone administration, the levels increased in five patients and overall values for the group averaged 8.1 ± 4.3 AU/mL, approaching the level measured during concurrent administration.

Activity of Factor VIII

Figure 4 shows the changes in factor VIII concentration concomitant with discontinuation of benzbromarone administration. Because factor VIII is not vitamin K dependent, its activity is not directly related to the action of warfarin. The average value of this parameter was 114.9 ± 38.2% during concurrent administration, 112.3 ± 34.7% after benzbromarone administration had been discontinued for 1 week, and 109.4 ± 36.5% after resumption of benzbromarone administration, thus changes in this parameter were not significant.

Total Plasma Warfarin Concentration

Figure 5 shows changes in total plasma warfarin concentration after discontinuation of benzbromarone. The values measured during concurrent administration averaged 569.7 ± 204.8 ng/mL, but after benzbromarone administration had been discontinued for 1 week, this level had decreased in six patients, with overall values averaging 496.7 ± 182.1 ng/mL (12.8% decrease). This difference was significant ($P < 0.05$). After resumption of benzbromarone administration, the levels increased in six patients and overall values for the group averaged 508.7 ± 171.3 ng/mL. This also represented a significant difference from levels measured 1 week after discontinuation of benzbromarone ($P < 0.05$).

Concentration of Free Warfarin

Figure 6 shows changes in free warfarin concentration after discontinuation of benzbromarone. The average value of this parameter was 2.0 ± 0.7 ng/mL during concurrent administration, 1.9 ± 0.7 ng/mL after benzbromarone administration had been discontinued for 1 week, and 1.9 ± 0.7 ng/mL after re-

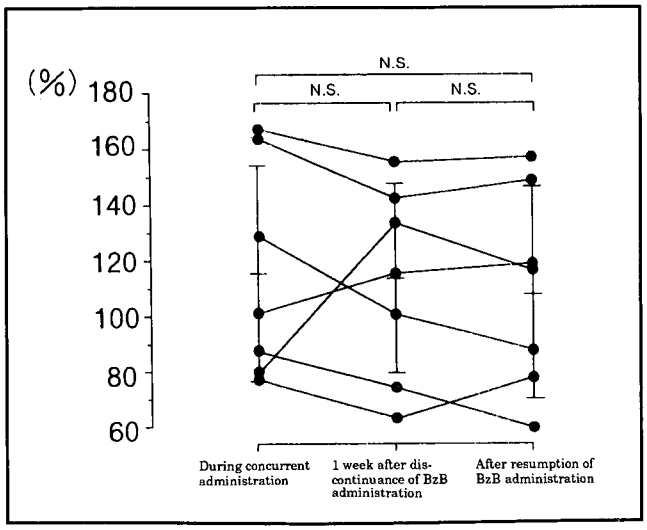

Figure 4. Changes in activity of coagulation factor VIII after discontinuation of benzbromarone administration in patients concurrently treated with warfarin potassium and benzbromarone: (1) during concurrent administration; (2) 1 week after discontinuation of benzbromarone; and (3) after resumption of benzbromarone administration. Bars indicate mean ± standard deviation; NS, not significant by the Wilcoxon test. BZB, benzbromarone.

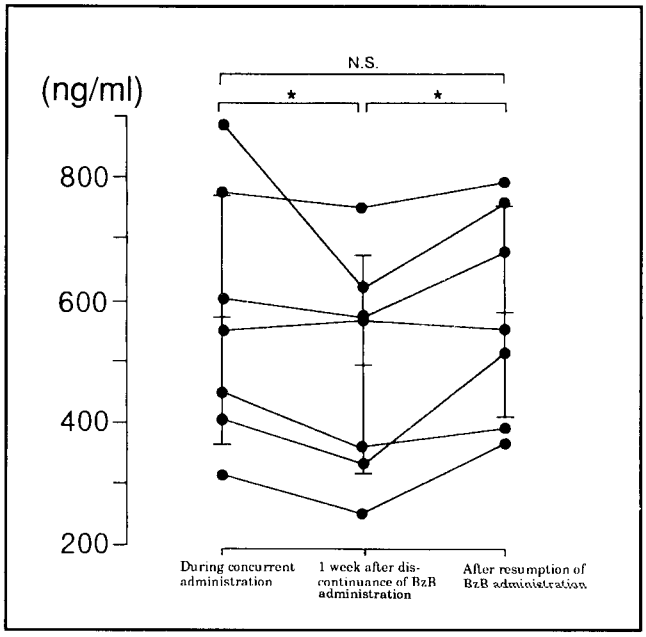

*Figure 5. Changes in total plasma concentration of warfarin after discontinuation of benzbromarone administration in patients concurrently treated with warfarin potassium and benzbromarone: (1) during concurrent administration; (2) 1 week after discontinuation of benzbromarone; and (3) after resumption of benzbromarone administration. Bars indicate mean ± standard deviation; * $P < 0.05$; NS, not significant by the Wilcoxon test. BZB, benzbromarone.*

sumption of benzbromarone administration; thus, almost no changes occurred.

DISCUSSION

Very few reports on the interaction between warfarin and benzbromarone have appeared; one exception is the study by Hadama et al,[14] which found that hemorrhagic tendencies developed in some patients concurrently receiving benzbromarone during a course of anticoagulant therapy with warfarin after prosthetic valve replacement. We also have encountered hemorrhagic tendencies, including gastrointestinal bleeding and hematuria, together with pronounced drops in thrombotest values in two patients treated with benzbromarone for gout during a course of anticoagulant therapy (data not shown), and accordingly embarked on the present study.

Warfarin impedes the production of the reduced form of vitamin K in the metabolic cycle of this vitamin. As a consequence, carbon dioxide is not introduced into the precursors of the various coagulation factors, and this increases the formation of coagulation factors without actual coagulative activity, i.e., PIVKA-II. Hence, anticoagulant action is manifested.[15] Thus, warfarin inhibits the synthesis of vitamin K-dependent coagulation factors in the liver. The indices of warfarin anticoagulant activity considered in the present study comprised the thrombotest, widely employed in clinical examinations, the vitamin K-dependent coagulation factor II, and PIVKA-II. Moreover, for comparison, factor VIII, which is not vitamin K dependent, also was included in the measured parameters.

After discontinuation of benzbromarone administration, changes were apparent in all vitamin K-dependent factors. Benzbromarone exerts little direct effect on the blood coagulation systems, however.[16,17] In fact, there were few changes in values for factor VIII, which is not vitamin K-dependent, in this study. The above-mentioned findings demonstrate that concurrent use of warfarin and benzbromarone causes a more pronounced drop in coagulative function in comparison to administration of warfarin alone, and this indicates that the action of warfarin is enhanced by benzbromarone.

In this study of seven patients concurrently treated with the two drugs, concurrent administration of

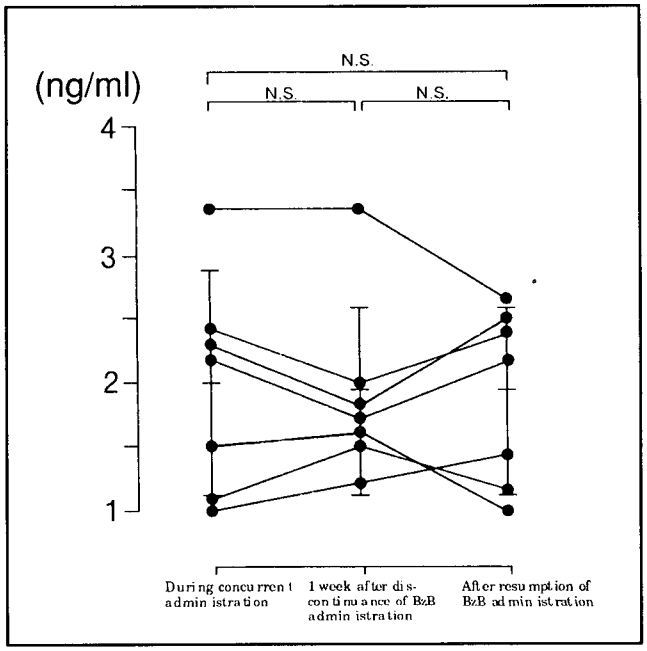

Figure 6. Changes in free concentration of warfarin after discontinuation of benzbromarone administration in patients concurrently treated with warfarin potassium and benzbromarone: (1) during concurrent administration; (2) 1 week after discontinuation of benzbromarone; and (3) after resumption of benzbromarone administration. Bars indicate mean ± standard deviation; NS, not significant by the Wilcoxon test. BZB, benzbromarone.

57.1 ± 18.9 mg/day of benzbromarone permitted maintenance of the thrombotest values at a level of 24.7 ± 6.4%, within the therapeutic range, with a comparatively small warfarin dosage of 1.8±0.7 mg/day. Thus, the results indicate an intense potentiation of warfarin action by this combined regimen.

To obtain information relating to the mechanism of interaction of these two drugs, the concentrations of both total plasma warfarin and free warfarin were measured. After 1 week of withdrawal of benzbromarone, there was a significant decrease in the total plasma concentration of warfarin. This suggests that concurrent administration of benzbromarone decreases warfarin clearance.

One conceivable mechanism that might explain the interaction of these two drugs is inhibition of hepatic drug metabolizing enzymes. One study of the interaction of warfarin and the uricosuric agent sulfinpyrazone[1] found that the action of warfarin is enhanced by a drop in warfarin clearance. This finding was attributed to the inhibition of the hydroxylation involved in the action of cytochrome P-450, an enzyme metabolizing the physiologically potent enantiomer (S)-warfarin. This process has not been fully clarified in relation to the metabolism of benzbromarone in humans, but the principal metabolites detected in plasma and urine are said to be monohydroxilated benzbromarone.[18,19] The metabolic enzyme cytochrome P-450 also may be involved in this process. Therefore, competition for metabolic enzymes could also have caused the observed elevation in plasma warfarin levels.

The total plasma warfarin concentration after a 1-week discontinuation of benzbromarone was found to be significantly lower than that measured during concurrent administration of the two drugs, showing a mean decrease of 12.8%. On the other hand, greater changes were noted in mean thrombotest value, which increased by 91.5%, factor II activity, which increased by 26.3%, and PIVKA-II concentration, which decreased by 29.3%. In clinical practice, warfarin is only administered as a racemic mixture, but the (S)-warfarin enantiomer is said to possess five times the anticoagulant activity of (R)-warfarin.[20] The fact that changes in the vitamin K-dependent coagulative system were more pronounced than changes in the total (racemic) plasma warfarin concentration could be explained by the assumption that the warfarin–benzbromarone interaction is, like the warfarin–sulfinpyrazone interaction, due to inhibited clearance of only the physiologically potent (S)-warfarin.

However, warfarin readily binds to serum albumin; in fact, 97% of warfarin transferred into the blood is bound to albumin and circulates in inactive form.[21,22] Consequently, if the protein-binding factor of a concurrently administered drug is high, then this drug replaces warfarin on the serum albumin binding sites, thereby increasing the quantity of free warfarin and thus enhancing warfarin action. Interactions caused by this type of mechanism are well known with respect to phenylbutazone.[20] On the other hand, benzbromarone is also readily bound to serum albumin, and the albumin-bound form is said to constitute more than 99% of the plasma content of this drug.[18] In view of these facts, changes in free warfarin concentration were also investigated in the present study. Almost no change in the mean free warfarin concentration was observed one week after discontinuation of benzbromarone administration, however. This finding indicates that competition for protein binding sites between warfarin and benzbromarone is unlikely to be significantly involved in the present interaction.

For all parameters that were significantly different after discontinuation of benzbromarone administration, mean values measured an average of 24.9 days after resumption of benzbromarone administration approached those measured before discontinuation of benzbromarone. However, a still longer period is regarded as necessary for stable reversion of the coagulation system to its original state. Subsequent examination revealed that in six patients the mean thrombotest value (26.3%) was elevated by 6.6% an average 86.7 days after resumption of benzbromarone administration, and thus had nearly reverted to the original level. In the remaining patient (patient 6 in Table I), benzbromarone administration was discontinued for therapeutic reasons 30 days after resumption; however, during the original period of concurrent administration, 2.5 mg/day of warfarin and 50 mg/day of benzbromarone were being administered, and the thrombotest value had been stabilized at 30%. After discontinuation of benzbromarone, despite an increased warfarin dosage of 4 mg, the thrombotest value rose to the high level of 43%. This case also appears to demonstrate the potent warfarin-enhancing action of benzbromarone.

It has been reported in population-based studies[23] and studies of family groups[24] that benzbromarone metabolism is genetically very slow in some individuals. In such individuals the effect of benzbromarone on the pharmacokinetics of warfarin is a particular concern. In addition, warfarin is known to interact not only with benzbromarone but also with other main uricosuric agents, and is known to be potentiated by the inhibition of drug metabolizing enzymes and competition of plasma protein. Caution therefore should be observed when warfarin and other uricosuric agents are used in combination.

We concluded that concurrent administration of warfarin and benzbromarone results in decreased levels of vitamin K-dependent coagulation factors and pronounced enhancement of the anticoagulant action of warfarin. This enhancing effect was attributed to a benzbromarone-induced decrease in warfarin clearance. Warfarin and benzbromarone are concurrently used with particular frequency in the field of cardiovascular medicine and surgery. Hence, due consideration must be devoted to the prevention of grave hemorrhagic tendencies in patients receiving concurrent benzbromarone during anticoagulant therapy.

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