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Usefulness of coadministration of bucolome in warfarin therapy: pharmacokinetic and pharmacodynamic analysis using outpatient prescriptions

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Abstract

Bucolome, a nonsteroidal anti-inflammatory drug, has often been coadministered to patients who take warfarin as an anticoagulant. This combination increases the anticoagulant effect, which is most likely due to the interaction of bucolome with the pharmacokinetics (PK) or pharmacodynamics (PD) of warfarin. More than 30 years ago the mechanism of this interaction was reported to be inhibition of warfarin protein binding by bucolome, and the inhibition of warfarin metabolism by bucolome was also recently reported. Here, we examined daily doses of warfarin and its anticoagulant effect (thrombo-test, TT) in outpatient prescriptions in five hospitals to elucidate the drug interaction and the usefulness of this drug combination. Among the warfarin prescriptions, 78 were for patients also taking bucolome and 99 were for patients not taking bucolome. The daily dose of warfarin in patients taking bucolome was significantly lower than those without bucolome (ca. 40%). TT in patients taking bucolome was significantly lower as compared to those not taking bucolome. Control of the anticoagulant effect was greater with coadministration of bucolome and warfarin than with warfarin alone. PK and PD analysis of our results suggests that the improved therapeutic effect resulting from coadministration of warfarin with bucolome was due to lower and less patient-to-patient variation of intrinsic hepatic clearance (CL_{int}) of warfarin, since bucolome decreased the high CL_{int} but did not have a great effect on the low CL_{int}.

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In conclusion, administration of bucolome in warfarin therapy is useful to control the anticoagulant effect of warfarin. Attention should also be paid to the enzymatic inhibition by bucolome on the PK of coadministered drugs.

Keywords: Warfarin; Bucolome; Drug interaction; Enzyme inhibition; Pharmacokinetics; Pharmacodynamics

1. Introduction

Warfarin has been used all over the world for decades for prevention and treatment of thrombus and embolism as an anticoagulant, and it is still an essential drug today. Warfarin, however, interacts with many other drugs (Koch-Weser and Sellers, 1971; MacLeod and Sellers, 1976; Deykin, 1970), so the optimization of dosage regimen is very difficult. Then, thrombo-test (TT) is generally used in Japan in the warfarin therapy, since TT values was found to be more useful than prothrombin time to control the anticoagulant activity during warfarin therapy in patients (Ikuma et al., 1999; Numata et al., 2001).

Bucolome has often been coadministered to patients who take warfarin. The coadministration ratio of warfarin and bucolome is extremely high in Niigata prefecture (ca. 300 km north from Tokyo, border on the Japan Sea) compared to other region and prefectures in Japan. Bucolome is a nonsteroidal anti-inflammatory drug. It is used for remission of inflammation and tumefaction after surgical operation and external injury. It is also applied for anti-inflammation, analgesic and antipyretic in rheumatoid arthritis, arthrosis deformans, cystitis, erythema exsudativum multiforme, acute sinusitis, acute otitis media and uterus adnexitis. Bucolome also decreases plasma uricate (uric acid) level in gout patients. Although application of bucolome should be limited to these uses, it is often administered to patients during warfarin therapy. Most of the patients who take warfarin in Niigata take bucolome, whereas those in the other areas do not. Therefore, patients who move in or out of Niigata may have trouble in their dosage regimen of warfarin.

Adequate information is found in the drug information sheets both in warfarin and bucolome preparations. Deliberate coadministration of bucolome with warfarin was reported to reduce the warfarin dose, and a steady therapeutic effect of warfarin was obtained. For example, Matsuoka (1977) reported that TT was maintained at about 15% when bucolome (300–600 mg/day) was used together with warfarin (1.0–1.5 mg/day). Sakashita et al. (1978) reported the usefulness of coadministration of bucolome in warfarin therapy in patients who had undergone operation to have an artificial valve placed in the heart. Sakuragawa et al. (1982) reported easier control of anticoagulant activity (TT = 10–25%) of warfarin at a daily dose of 1–2 mg/day with coadministration of bucolome (300 mg/day) than warfarin therapy without bucolome in similar patients. The mechanism by which bucolome increases the warfarin effect is interesting. Matsuoka (1977) reported that albumin-unbound warfarin in plasma was increased by coadministration of bucolome, which has a higher affinity to plasma albumin. In addition, Majima et al. (1982) found that protein binding of warfarin was decreased by bucolome. While these two explanations differ, they both indicate that the interaction between warfarin and bucolome is related to protein binding. On the other hand, Takahashi et al. (1999) noted that inhibition by bucolome of 7-oxidation on cytochrome P-450 (CYP) 2C9 to (*S*)-warfarin, which shows a higher pharmacological effect than (*R*)-warfarin, was important, in addition to the interaction related to protein binding.

We therefore examined daily doses of warfarin and its anticoagulant effect (TT) from outpatient prescriptions in five hospitals in different parts of Japan (Niigata, Toyama and Saitama prefectures) to elucidate the drug interaction and the mechanism of this drug combination. Usefulness and risk of the combination of bucolome with warfarin were evaluated by pharmacokinetic (PK) and pharmacodynamic (PD) analysis of warfarin.

2. Theoretical

2.1. PK of warfarin

Because the biological half-life of warfarin is very long (Holford, 1986), orally repeated administration of the drug shows small peaks and troughs in the time course of plasma level. Since warfarin is eliminated

mostly by liver metabolism (Banfield et al., 1983), the total body clearance of the drug is similar to hepatic clearance. In addition, the liver extraction rate of warfarin is too low to be classified as a low extraction drug. The fraction of warfarin that permeates through the gastrointestinal duct against the total amount administered is almost 100%, and no metabolism of warfarin was found in the intestinal mucosa during the absorption process (Banfield et al., 1983; Shetty et al., 1989). Thus, steady-state blood concentration of warfarin, C_{ss}, during the repeated administration of dose, D, and dosage interval, τ, is expressed in Eq. (1) and for the protein unbound level, $C_{ss,f}$ is expressed in Eq. (2) as follows:

$$C_{SS} = \frac{FD/\tau}{CL_{tot}} = \frac{F_h D/\tau}{CL_h} = \frac{D/\tau}{fCL_{int}} \quad (1)$$

$$C_{SS,f} = C_{SS} f = \frac{fFD/\tau}{CL_{tot}} = \frac{fF_h D/\tau}{CL_h} = \frac{D/\tau}{CL_{int}} \quad (2)$$

where F and F_h are the extent of bioavailability and evasion ratio to hepatic metabolism, CL_{tot}, CL_h and CL_{int} are total body clearance, hepatic clearance and hepatic intrinsic clearance, and f is the unbound ratio to protein binding in blood of warfarin.

In Eqs. (1) and (2), PK parameters related to change in warfarin blood level caused by coadministration of bucolome are only f and CL_{int}. When f for warfarin is increased by interaction of protein binding by bucolome, C_{ss} decreases, whereas $C_{ss,f}$, which is directly related to the pharmacological effect of warfarin, does not change, as shown by Eqs. (1) and (2). These equations suggest that enzymatic inhibition by bucolome, as mentioned by Takahashi et al. (1999), may be the mechanism for the warfarin-bucolome interaction, and that plasma protein binding is not the mechanism.

2.2. PD of warfarin

Warfarin does not work in the blood circulation, but shows an anticoagulant effect by inhibiting the Vitamin K-dependent coagulant factor in the liver. Thus, the anticoagulant effect of warfarin appears a few days after starting the warfarin therapy (Vesell and Shively, 1974). Warfarin inhibits the synthesis of blood coagulation factors such as prothrombin to decrease prothrombin activity and show an anticoagulant effect. Thus, PD of warfarin is shown using the indirect response model (Jusko and Ko, 1984) as follows:

$$\frac{dR}{dt} = k_{in}\left[1 - \frac{C}{IC_{50} + C}\right] - k_{out}R \quad (3)$$

where R is the physiological effect (prothrombin activity), k_{in} and k_{out} are rate constants to and from the effective sites, respectively, showing the physiological effect, and IC_{50} is the warfarin concentration showing 50% inhibition to the physiological effect. The pharmacological effect of warfarin is directly related to the protein-unbound blood level, $C_{ss,f}$, as mentioned before. Thus, Eq. (3) can be transformed as follows:

$$\frac{dR}{dt} = k_{in}\left[1 - \frac{C_{SS,f}}{IC_{50,f} + C_{SS,f}}\right] - k_{out}R \quad (4)$$

where the subscript f shows parameters related to the protein-unbound fraction of warfarin. Since the pharmacological effect, R, must be constant during the repeated administration of warfarin, dR/dt in Eqs. (3) and (4) can be substituted by zero. Thus, a relationship between $C_{ss,f}$ and prothrombin activity, R, is shown as the following equation:

$$C_{SS,f} = \frac{k_{in}IC_{50,f}}{k_{out}R} - IC_{50,f} \quad (5)$$

From the equation, $C_{ss,f}$ can be determined by measuring prothrombin activity.

3. Methods

3.1. Survey of prescriptions and TT values

Patients with prescriptions for warfarin were selected from outpatients in five hospitals, as shown in Table 1. Number of patients is 177. Their ages were in the range of 42–86 (mean ± S.D.: 68 ± 11), and 70% were male among them. Most patients had basal diseases such as ischemic heart disease, valvular disease, arteriosclerosis obliterans, and they had complications of heart failure, hypertension, diabetes, hyperlipemia and so on.

The daily dose of warfarin, coadministration of bucolome, and other coadministered drugs were examined. In addition, TT values were examined in the patients at least 2 weeks after starting the warfarin therapy. Bucolome was frequently coadministered with warfarin (75/81 patients) in Niigata Prefectural-Kakizaki

Table 1
The prescriptions containing warfarin extracted from prescriptions for out-patients in five hospitals

Hospitals	Period of survey	Number of prescriptions	
		With bucolome	Without bucolome
Niigata Prefectural Kakizaki Hospital	October–November 1998	26	3
Niigata Prefectural Muikamachi Hospital	November–December 2000	19	3
Sekishinkai Sayama Hospital	November 1997–May 2001	30	0
Hokuriku Central Hospital	June–July 2000	1	30
Himi Municipal Hospital	July–August 2000	2	63
Total		78	99

Hospital and Muikamachi Hospital (Niigata pref.) and Sekishinkai Sayama Hospital (Saitama pref.). On the other hand, bucolome was seldom coadministered with warfarin (3/96 patients) in two hospitals in Toyama prefecture (Hokuriku Central Hospital and Himi Municipal Hospital) (Toyama prefecture is located west of Niigata prefecture).

3.2. Calculation of intrinsic hepatic clearance

Since TT can be replaced with prothrombin activity, R, in the evaluation of the pharmacological effect of warfarin, $C_{ss,f}$, was calculated by substituting TT (%) for R in Eq. (5). In addition, IC_{50}, f, k_{in} and k_{out} were obtained from a previous report (Jusko and Ko, 1984), and $IC_{50,f}$ was calculated from IC_{50} and f. Next the intrinsic hepatic clearance, CL_{int}, in each patient was calculated by substituting $C_{ss,f}$ in Eq. (2).

3.3. Statistical analysis

The statistical analysis of the difference between different treatments was carried out using the unpaired Student's t-test. A level of probability of 0.05 was taken as the level of significance.

4. Results

Fig. 1 shows a histogram of the daily dose of patients taking warfarin alone or warfarin and bucolome (78 and 99 patients, respectively). The daily dose of warfarin in patients who also took bucolome was about 40% of those who did not take bucolome, and the dose was significantly lower than the dose without bucolome ($p < 0.05$). Fig. 2 shows a histogram of TT values. The therapeutic range of TT values (about 8–15%) was obtained in about 50% patients by coadministration of bucolome, whereas TT values for more than 80% patients were over the therapeutic range for warfarin therapy without bucolome. The TT values in patients who took bucolome were significantly lower than those who did not take bucolome ($p < 0.05$).

Fig. 3 shows the relationship between daily dose of warfarin and the TT value in each patient. The meshed part in the figure shows the therapeutic range of warfarin. The daily dose of warfarin in the coadministration group with bucolome was much lower than that without bucolome. In addition, TT values in the coadministration group

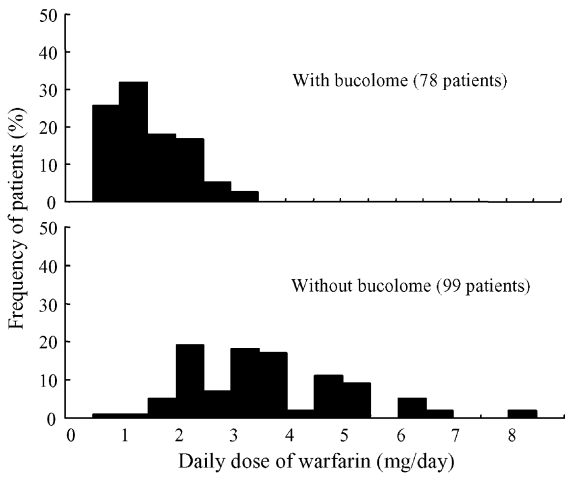

Fig. 1. Histogram of the daily dose of warfarin in patients who took or did not take bucolome (78 and 99 patients, respectively).

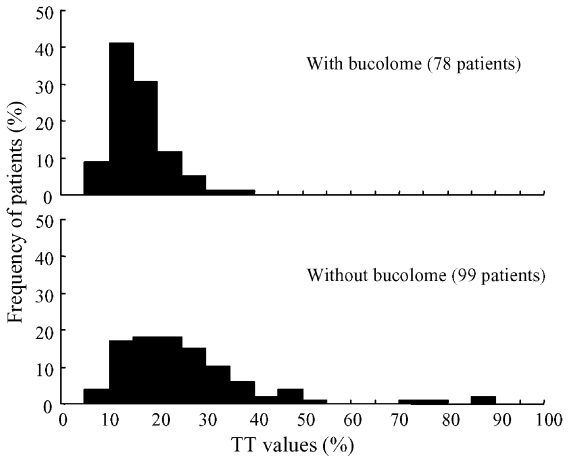

Fig. 2. Histogram of TT values in patients who took or did not take bucolome (78 and 99 patients, respectively).

with bucolome show less variation than that without bucolome.

CL_{int} of warfarin in each patient was calculated from these results, as described in Section 2. Fig. 4 shows a histogram of the calculated CL_{int}. The histogram of CL_{int} was expressed every 1.0 L/day, from 0 to 390 L/day. CL_{int} of warfarin in the group with bucolome was significantly lower than that without bucolome ($p < 0.05$).

All coadministered drugs with warfarin, except bucolome, were examined for their effect on warfarin therapy, and these drugs were classified into the following groups according to the drug-drug interaction documents supplied by each pharmaceutical company: those

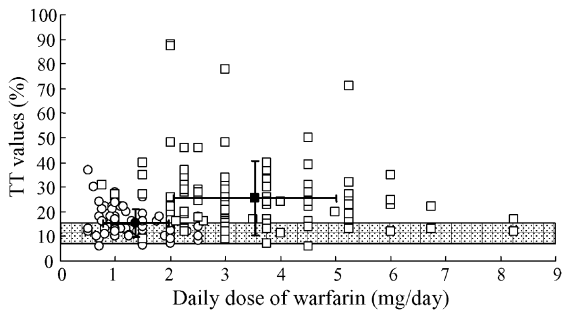

Fig. 3. The relationship between daily dose of warfarin and TT values in each patient. The meshed part shows the treatment level of warfarin (TT: 8–15%). (◯) With bucolome (78 patients). (□) Without bucolome (99 patients). (●) Average ± S.D. (with bucolome). (■) Average ± S.D. (without bucolome).

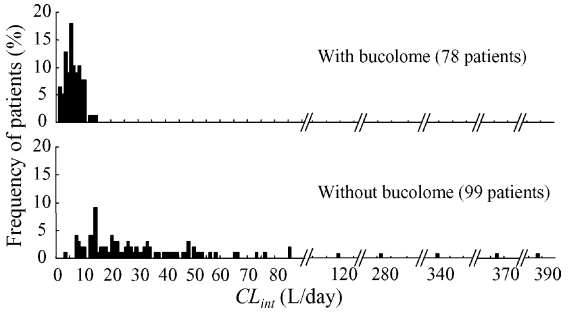

Fig. 4. Histogram of the calculated CL_{int}. CL_{int} expressed every 1.0 L/day, from 0 to 390 L/day.

that increased the warfarin effect, those that decreased the warfarin effect and those that caused no interaction. Each daily dose (D), TT value and CL_{int} of warfarin was compared between groups with and without bucolome coadministration. No significant differences in D, TT value or CL_{int} were found among the three groups, suggesting that other coadministered drugs besides bucolome did not affect these values (Table 2).

5. Discussion

The present calculation of CL_{int} of warfarin suggests that the interaction between warfarin and bucolome was caused by inhibition of metabolic reaction to warfarin by bucolome. Therefore, sufficient efficacy of warfarin with coadministration of bucolome was obtained even with a low dose of warfarin by its high protein-unbound level. In addition, the difference between peak and trough levels of warfarin became smaller because of an increase in biological half-life. Therefore, the time-dependent change of warfarin efficacy, or the TT value, should be smaller. Furthermore, it is suggested that the anticoagulant effect of warfarin was satisfactorily controlled because the patient-to-patient variation of the TT value decreased as a result of the decreased interindividual variation of CL_{int} of warfarin by addition of bucolome.

The present survey of warfarin prescriptions suggested that most drugs other than bucolome did not affect warfarin therapy, whether or not they were listed as drugs that interacted with warfarin.

However, the following problems remained in the present methods. The first problem is the difference of

Table 2
All coadministered drugs with warfarin except for bucolome

	With bucolome				Without bucolome			
	n	*D* (mg/day)	TT (%)	CL_{int} (L/day)	*n*	*D* (mg/day)	TT (%)	CL_{int} (L/day)
Drugs increasing the warfarin effect								
Aspirin	22	1.62 ± 0.68	16.1 ± 6.7	7.68 ± 3.21	25	3.43 ± 1.21	22.3 ± 9.6	25.86 ± 12.88
Other NSAIDs	4	1.10 ± 0.08	17.4 ± 5.3	6.19 ± 2.12	6	4.00 ± 1.69	29.6 ± 11.0	46.48 ± 26.85
Ticlopidine hydrochloride	4	2.00 ± 0.70	12.9 ± 3.4	7.79 ± 3.38	14	3.62 ± 1.01	37.7 ± 24.5	98.89 ± 126.3
Other antiplatelet	16	1.55 ± 0.72	13.3 ± 3.5	6.47 ± 3.86	11	2.90 ± 1.38	30.1 ± 12.8	35.74 ± 31.60
Antihyperlipidemic drugs	13	1.29 ± 0.50	16.1 ± 8.9	6.00 ± 2.93	18	3.90 ± 1.19	27.0 ± 20.8	65.71 ± 110.1
Oral antidiabetic	3	1.05 ± 0.13	19.7 ± 4.0	7.00 ± 2.43	14	3.41 ± 1.28	25.1 ± 7.1	30.97 ± 14.71
Allopurinol	1	1	12.8	3.88	10	3.58 ± 1.14	19.3 ± 9.4	24.74 ± 18.80
Benzbromarone	0	–	–	–	1	2.25	37	34.96
Prednisolone acetate	0	–	–	–	3	2.50 ± 0.43	29.3 ± 16.1	28.85 ± 19.63
Thiamazole	2	1.15	14.5	4.48	0	–	–	–
Levothyroxine	2	1.2	13.5	4.86	2	3.75	13	14.82
Propafenon hydrochloride	0	–	–	–	4	2.42 ± 1.18	49.3 ± 33.6	150.5 ± 206.4
Cisapride	2	1.25	24.8	11.0	3	5.31 ± 1.97	16.8 ± 6.0	29.28 ± 15.25
Tranilast	1	1	17	5.42	0	–	–	–
Cefdinir	1	1.2	20	7.94	0	–	–	–
Clarithromycin	1	0.75	16	3.78	0	–	–	–
Imipramine hydrochloride	1	1.3	16	6.55	0	–	–	–
Drugs decreasing the warfarin effect								
Spironolactone	7	1.16 ± 0.58	15.1 ± 3.4	5.86 ± 3.63	9	3.86 ± 2.24	22.3 ± 11.5	27.07 ± 12.69
Others								
Digitalis preparations	34	1.34 ± 0.55	14.6 ± 4.1	6.15 ± 2.83	34	3.50 ± 1.66	24.1 ± 12.3	35.14 ± 48.64
Nitrates	31	1.27 ± 0.56	15.0 ± 6.3	5.61 ± 2.65	40	3.48 ± 1.38	26.4 ± 14.6	42.57 ± 63.24
Ca antagonists	39	1.23 ± 0.50	16.3 ± 6.3	6.10 ± 2.57	54	3.54 ± 1.63	24.3 ± 14.3	38.91 ± 66.27
β-blockers	11	1.60 ± 0.70	15.5 ± 5.8	7.35 ± 3.19	11	3.18 ± 0.79	22.0 ± 8.64	24.04 ± 11.85
ACE inhibitors	17	1.15 ± 0.50	17.1 ± 7.6	6.16 ± 3.13	23	3.62 ± 1.23	19.0 ± 8.9	24.04 ± 15.93
Loop diuretics	41	1.32 ± 0.59	14.9 ± 4.0	6.00 ± 2.65	48	3.79 ± 1.65	23.5 ± 11.9	34.51 ± 40.62
Other cardiovascular preparations	20	1.67 ± 0.47	15.6 ± 4.3	8.12 ± 2.83	45	3.55 ± 1.71	24.4 ± 13.4	35.52 ± 55.80
H_2-blocker (except for Cimetidine)	14	1.44 ± 0.66	16.1 ± 5.2	7.17 ± 3.20	40	3.54 ± 1.22	26.1 ± 16.7	47.39 ± 79.33
Other digestive drugs	34	1.22 ± 0.55	16.2 ± 7.1	5.81 ± 2.71	28	2.81 ± 1.36	29.4 ± 19.1	47.70 ± 85.38
Respiratory drugs	7	1.03 ± 0.27	18.8 ± 4.60	6.52 ± 2.73	15	3.05 ± 1.59	24.9 ± 9.9	29.38 ± 22.38
Benzodiazepine derivatives	11	1.22 ± 0.58	16.9 ± 6.9	6.41 ± 3.49	32	3.55 ± 1.59	24.0 ± 13.1	36.27 ± 49.63
Others	28	1.18 ± 0.49	17.2 ± 4.7	6.67 ± 3.35	28	3.64 ± 1.88	30.2 ± 19.7	66.23 ± 104.6
All coadministered drugs (except for bucolome)	367	1.36 ± 0.60	15.5 ± 5.7	6.40 ± 2.89	518	3.53 ± 1.49	25.6 ± 15.1	42.40 ± 65.88

Each value represents the mean ± S.D.

the monitoring interval of TT and the adjustment of the warfarin dose among doctors. There is some possibility that good control of TT values is obtained by doctors who frequently monitor TT values and adjust warfarin dose with a combination of bucolome.

The next problem is difference in the pharmacological effects between (*S*)-warfarin and (*R*)-warfarin. Although we did not evaluate the difference of (*S*)- and (*R*)-warfarin in this study, the strength of the anticoagulant effect, the unbound ratio to protein binding and the metabolic mechanism may be different between them. These problems must be considered in the future. Furthermore, the appearance of the anticoagulant effect of warfarin greatly relates to age of patients, and CL_{int} may also be dependent on the age and/or basic diseases. Thus we must consider these individual differences. However, we assumed that patients had little variation in the present study, since age of the outpatient subjects in this study has little variation (68 ± 11).

In conclusion, it is suggested that interaction between warfarin and bucolome was caused by bucolome inhibiting the main metabolic enzyme (CYP2C9) of (*S*)-warfarin. CYP2C9 is polymorphic, suggesting that issues for extensive and poor metabolizers should be considered in the warfarin therapy. In spite of some problems in the present evaluation, in patients who did not obtain therapeutic control by warfarin alone bucolome-coadministration therapy is an available and useful method to satisfactorily control the anticoagulant effect of warfarin.

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