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Comparative Pharmacokinetics of Coumarin Anticoagulants XXXV: Examination of Possible Pharmacokinetic Interaction between (*R*)-(+)- and (*S*)-(−)-Warfarin in Humans

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Abstract □ The elimination kinetics and anticoagulant effect produced by single 1.5-mg/kg doses of (*R*)-(+)-, (*S*)-(−)-, and racemic warfarin were determined in 10 healthy men. The results obtained in experiments with the individual enantiomers were used to predict the elimination kinetics and anticoagulant effect of racemic warfarin, assuming that there is no interaction between the two enantiomers. These predictions were compared to experimental results, and no significant differences were observed. This finding suggests that there are no pronounced pharmacokinetic or pharmacodynamic interactions between single large doses of (*R*)-(+)- and (*S*)-(−)-warfarin in humans.

Keyphrases □ Warfarin—(*R*)-(+)- and (*S*)-(−)-forms, elimination kinetics and anticoagulant effect compared, humans □ Elimination kinetics—(*R*)-(+)- and (*S*)-(−)-warfarin compared, humans □ Anticoagulant effect—(*R*)-(+)- and (*S*)-(−)-warfarin compared, humans □ Pharmacokinetics—(*R*)-(+)- and (*S*)-(−)-warfarin compared, humans □ Enantiomers—(*R*)-(+)- and (*S*)-(−)-warfarin, elimination kinetics and anticoagulant effect compared, humans

The anticoagulant warfarin is used therapeutically in the racemic form. The constituents of the racemic mixture, (*R*)-(+)- and (*S*)-(−)-warfarin, differ in pharmacokinetic characteristics, anticoagulant potency, and metabolic fate (1–9). The plasma warfarin concentrations of rats after intravenous administration of a dose of racemic warfarin are essentially equal to the sum of the concentrations observed after separate administration of half of the dose of each individual enantiomer, suggesting that one enantiomer does not measurably affect the pharmacokinetics of the other (8). On the other hand, Chan *et al.* (3) observed that the metabolic pattern of single doses of racemic warfarin in humans is not equivalent to the sum of the patterns obtained from administration of the individual enantiomers, suggesting an interaction between the two enantiomers (3).

To examine the possible pharmacokinetic and pharmacodynamic implications of the apparent metabolic interaction in humans, the kinetics of elimination and anticoagulant effect of a single dose of racemic warfarin were compared with the kinetics predicted on the basis of results obtained by separate administration of the individual enantiomers.

EXPERIMENTAL

Ten healthy men, 21–51 years old, received single oral doses of (*R*)-(+)-, (*S*)(−)-, and racemic warfarin, 1.5 mg/kg, at intervals of at least 1 month. Daily blood samples were obtained for 9 days, and the warfarin concentration and the prothrombin complex activity were determined in plasma. Details of these procedures were described previously (9).

The apparent volume of distribution, V_d, the elimination rate constant, k_{el}, and the total body clearance, *TC*, were determined (10), and the synthesis rate of prothrombin complex activity, R_{syn}, was calculated (11). The pharmacokinetic and pharmacodynamic data obtained following separate administration of the two enantiomers were used to make quantitative predictions of pharmacokinetic and pharmacodynamic patterns of single doses of racemic warfarin (6, 8).

RESULTS AND DISCUSSION

The total body clearances of (*R*)-(+)- and (*S*)-(−)-warfarin were 1.30 ± 0.47 and 2.08 ± 0.70 ml/hr/kg (mean ± *SD*), respectively. The individual data are reported elsewhere (10). The experimentally determined and predicted individual values of k_{el}, V_d, and *TC* for racemic warfarin are presented in Table I. There were no statistically significant differences between the experimental and predicted values; the correlation between

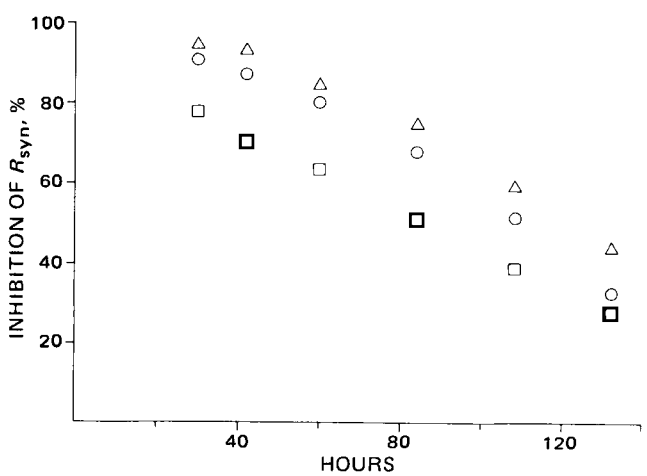

Figure 1—*Time course of inhibition of prothrombin complex activity synthesis rate, R_{syn}, produced by a single oral 1.5-mg/kg dose of* (S)-(−)-*warfarin* (△), *racemic warfarin* (○), *and* (R)-(+)-*warfarin* (□). *Average of data from 10 subjects.*

Table I—Experimentally Determined and Predicted Pharmacokinetic Constants for the Elimination of a Single Dose of Racemic Warfarin, 1.5 mg/kg, by Healthy Men

Subject	Elimination Rate Constant, hr^{-1}		Volume of Distribution, ml/kg		Total Body Clearance, ml/hr/kg	
	Experimental[a]	Predicted[b]	Experimental[a]	Predicted[b]	Experimental[a]	Predicted[b]
N-30	0.0162	0.0144	112	111	1.81	1.60
N-31	0.0138	0.0135	122	106	1.68	1.43
N-33	0.0157	0.0160	117	87	1.84	1.39
N-39	0.0172	0.0191	124	105	2.13	2.01
N-40	0.0186	0.0146	114	114	2.12	1.66
N-41	0.0136	0.0158	144	69	1.96	1.09
N-44	0.0171	0.0161	104	116	1.78	1.87
N-46	0.0144	0.0123	113	125	1.63	1.54
N-48	0.0146	0.0105	87	81	1.26	0.85
N-50	0.0193	0.0187	115	114	2.22	2.13
Mean	0.0161	0.0151	115	103	1.84	1.56
SD	0.0020	0.0027	51	18	0.29	0.40

[a] For a 1.5-mg/kg dose of racemic warfarin. [b] Simulated on the basis of a combined dose of (*R*)-(+)- and (*S*)-(−)-warfarin, 0.75 mg/kg each.

experimental and predicted *TC* values was significant ($r = 0.73$, $p < 0.02$).

The experimental and predicted values for percent inhibition of R_{syn} by racemic warfarin from 30 to 132 hr are listed in Table II. As reported previously, the predicted values differ somewhat depending on whether the calculations are made by first estimating the contribution of (*S*)-(−)-warfarin and then that of (*R*)-(+)-warfarin, or in reverse order, unless the slope of the R_{syn} *versus* log plasma concentration regression line of the two enantiomers is identical (6). Since these slopes are not identical in humans (10), the initial predictions were made by averaging the results of the two methods of calculation (Procedure A). As shown in Table II, these predictions yielded slightly higher values than were found experimentally, the differences being statistically significant at 30, 42, and 60 hr. On the other hand, excellent agreement was obtained between experimental and predicted values when the predicted values were calculated just by first estimating the contribution of the (*R*)-(+)-enantiomer and then estimating the contribution of the (*S*)-(−)-enantiomer (Procedure B).

The average time courses of inhibition of R_{syn} following administration of (*R*)-(+)-, (*S*)-(−)-, or racemic warfarin in single doses of 1.5 mg/kg are shown in Fig. 1. These data reflect the greater potency of (*S*)-(−)-warfarin despite its more rapid elimination than (*R*)-(+)-warfarin.

Table II—Experimentally Determined and Predicted Inhibition of Prothrombin Complex Activity Synthesis Rate, R_{syn}, after Oral Administration of a Single Dose of Racemic Warfarin, 1.5 mg/kg, to 10 Healthy Men

Hours	Inhibition of R_{syn}, % (mean ± *SD*)		
	Experimental	Predicted by Procedure A[a]	Predicted by Procedure B[a]
30	91 ± 6	98 ± 5[b]	97 ± 6
42	87 ± 4	96 ± 6[b]	92 ± 7
60	80 ± 5	86 ± 6[b]	81 ± 6
84	68 ± 15	71 ± 8	67 ± 9
108	52 ± 21	57 ± 12	53 ± 13
132	33 ± 19	43 ± 16	38 ± 17

[a] See *Results and Discussion* for difference between Procedures A and B. [b] Statistically significantly different from experimental mean value ($p < 0.05$).

The results of this investigation indicate that there are no pronounced pharmacokinetic or pharmacodynamic interactions between single doses of (*R*)-(+)- and (*S*)-(−)-warfarin in humans. The highest plasma concentrations observed in individual subjects following administration of racemic warfarin ranged from 7.6 to 11.9 μg/ml, considerably above the usual therapeutic concentration range of 1–2 μg/ml (12). Thus, the conditions of this investigation were favorable for eliciting a drug interaction on acute dosing. However, the results do not preclude the occurrence of a significant interaction between the enantiomers of warfarin during chronic administration.

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