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PHARMACOKINETICS AND DISPOSITION

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The effect of cimetidine on the steady-state pharmacokinetics and pharmacodynamics of warfarin in humans

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Abstract *Objective*: The interaction of multiple oral doses of cimetidine on the steady-state pharmacokinetics and pharmacodynamics of warfarin was investigated in six healthy male volunteers.
Methods: The subjects were given individually adjusted doses of warfarin to achieve therapeutic levels of prothrombin activity. The established daily maintenance oral dose of warfarin was kept stable throughout the trial and, on study days 8–14, each volunteer received a 800-mg daily dose of cimetidine. The degree of anticoagulant response produced by warfarin was quantified by the determination of both the prothrombin time and factor-VII clotting activity.
Results: Cimetidine co-administration had no significant effect on the pharmacokinetics of the more potent *S*-warfarin but significantly increased by 28% ($P < 0.05$) mean *R*-warfarin trough plasma concentrations and decreased by 23% ($P < 0.05$) mean *R*-warfarin apparent clearance. Both prothrombin time and factor-VII clotting activity displayed considerable inter-subject variability and were not significantly affected by concurrent cimetidine treatment. The reduction of apparent clearance of *R*-warfarin by cimetidine was found to be the effect of inhibition of the formation of warfarin metabolites as determined by apparent formation clearance values (±SD) of *R*-6-hydroxywarfarin (31.1 ± 7.4 ml/h baseline; 18.5 ± 4.5 ml/h at end of cimetidine treatment; $P < 0.01$), and *R*-7-hydroxywarfarin (6.9 ± 1.3 ml/h baseline; 4.3 ± 1.1 ml/h at end of cimetidine treatment; $P < 0.01$).
Conclusion: Cimetidine stereoselectively affects the steady-state pharmacokinetics of warfarin by inhibiting the disposition of the less potent *R*-warfarin in humans. However, this interaction is likely to be of minimal clinical significance in most patients.

Key words Warfarin · Cimetidine · Drug–drug interaction

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Introduction

Cimetidine, a substituted imidazole, is the first marketed H_2-receptor antagonist for the treatment of peptic ulcers [1, 2]. Cimetidine binds with cytochrome P_{450} enzymes and is thus an inhibitor of hepatic oxidative metabolism of a variety of drugs [3, 4, 5, 6]. The imidazole ring moiety within the cimetidine molecule is thought to be responsible for this inhibitory activity [7]. Although recognised as a general inhibitor, cimetidine does demonstrate some degree of specificity for individual cytochrome P_{450} isozymes, for example CYP1A2 [8] and CYP2C19 [9].

Commercially available warfarin is a racemic mixture of two enantiomers widely used as an oral anticoagulant with a narrow therapeutic index. The two enantiomers differ in both their pharmacokinetics and pharmacodynamics. The eutomer *S*-enantiomer is more potent as an anticoagulant than the *R*-enantiomer [10, 11] and has a shorter terminal half-life. Warfarin enantiomers are extensively metabolised in the liver by different cytochrome P_{450} isozymes [12, 13].

Cimetidine has been shown to potentiate the hypoprothrombinemic response to the oral anticoagulant warfarin in some patients [14, 15, 16]. As with many warfarin interactions, there is considerable interindivid-

ual variability in the magnitude of the interaction. The proposed mechanism of the interaction is the stereoselective reduction in the clearance of warfarin by inhibiting the oxidative metabolism of the less pharmacologically active *R*-warfarin to a greater extent than the more active *S*-warfarin [17, 18, 19].

In most detailed drug-interaction studies involving warfarin, it is administered as a large single dose during chronic administration of the interacting drug. Yet, warfarin is given clinically as a multiple-dose regimen. During a single-dose study, however, no statistically significant effect of cimetidine on the pharmacodynamics of warfarin could be demonstrated, although cimetidine was shown to impair the clearance of warfarin by inhibiting the metabolism of the less potent *R*-enantiomer [17, 18]. In general, multiple-dose studies are recognised as more sensitive in detecting drug–drug interactions than single-dose studies. The present study was conducted to assess the effect of chronically administered cimetidine on steady-state warfarin pharmacokinetics and pharmacodynamics as measured by prothrombin time and factor-VII clotting activity in six healthy adult male volunteers.

Methods

Study location

This study was conducted at the Clinical Unit of Medeval Ltd, University of Manchester. Prothrombin time was determined at the Northern Laboratory Services, Manchester. Determinations of factor-VII clotting activity, plasma concentrations of the warfarin enantiomers and urinary concentrations of warfarin metabolites were performed at the School of Pharmacy and Pharmaceutical Sciences, University of Manchester. Approval to conduct the study was obtained by an independent ethics committee. The study was performed in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving subjects. Written informed consent was obtained from each subject prior to participation in the study.

Subjects

Six healthy, male volunteers, aged between 18 years and 40 years were enrolled in the study. All volunteers were deemed healthy by premedical and postmedical examinations, which included medical history, physical examination, blood pressure measurement and electrocardiogram, urinalysis, and both routine biochemical and haematological examinations. Subjects had not taken any other drug for 7 days before the trial, during the trial or for the 4 days after the trial. Use of alcohol within 12 h prior to or during the course of the study was forbidden.

Study protocol

The study was of an open, longitudinal design, for which the subject served as his own control. Each volunteer received an initial 15-mg oral dose of racemic warfarin (3 × 5-mg Marevan tablets) on day 1. On day 3, the daily dose of warfarin was adjusted for each volunteer to achieve a therapeutic level of prothrombin activity, based on factor-VII measurements obtained up to 36 h after the initial dose of warfarin [20]. The established daily maintenance oral dose of warfarin was kept stable throughout the trial and, on days 8–14, each volunteer received an 800-mg daily dose of cimetidine (2 × 400 mg Tagamet tablets). On days of warfarin administration, the dose was taken along with 100 ml of water at 0830 hours. A further 100 ml of water was drunk within the next 30–45 s. Cimetidine was administered with 100 ml of water at 0815 hours. Citrated venous blood samples (5 ml) for the determination of prothrombin time and factor-VII clotting activity were drawn on three occasions, separated by at least 24 h, prior to and at 4, 12, 24, 36 and 48 h after the initial dose of warfarin; just before and at 4 h and 12 h after warfarin administration on days 7, 14 and 21 (where appropriate) and daily just before the dose of warfarin on all other days. Heparinised venous blood samples (6 ml) for the assay of warfarin enantiomers were collected immediately before and at 4, 12, 24 and 48 h after the initial dose of warfarin, every second day thereafter until the end of the study and immediately before and at 4, 12 and 24 h after warfarin administration on days 7, 14 and 21 (where appropriate). After a collection of a control sample, urine samples were collected during 24-h timed intervals on day 7 and day 14. The total volume of urine was recorded and an aliquot of each sample was stored at −20 °C pending analysis for warfarin metabolites.

Warfarin metabolites

Racemic 6-hydroxywarfarin and 7-hydroxywarfarin, *S*,*S*-warfarin alcohol and *R*,*S*-warfarin alcohol were synthesised as described previously [18]. The racemic internal standard (3-[α-(4′-fluorophenyl-)-b-acetyl]-4-hydroxycoumarin; 4′-fluorowarfarin) was a gift from Ciba-Geigy Ltd, Basle, Switzerland.

Analytic methods

The warfarin enantiomers in plasma and the various warfarin metabolites (*R*-6- and *R*-7-hydroxywarfarin, *S*-6- and *S*-7-hydroxywarfarin, *R*,*S*- and *S*,*S*-warfarin alcohols) in urine were determined using a stereospecific high-performance liquid chromatography (HPLC) assay with fluorescence detection [21]. Briefly, the assay method involves solvent extraction of plasma and urine samples containing the internal standard racemic 4′-fluorowarfarin, followed by coupling the warfarin enantiomers and their metabolites with carbobenzyloxy-L-proline in the presence of dicyclohexylcarbodiimide and imidazole. The diastereoisomers are separated on a silica HPLC column and then, after postcolumn amidolysis with *n*-butylamine, quantified by fluorescence detection. No interfering peaks were observed in control plasma and urine samples spiked with cimetidine.

Assessment of anticoagulant effect

Prothrombin time measurements were made using Quick's one-stage test [22]. Factor-VII-clotting-activity measurements were performed using a chromogenic amidolytic assay in citrated plasma [23]. The degree of anticoagulant effect was determined by measuring the area under the prothrombin-time- and the factor-VII-clotting-activity–time curves (AUC_{PT} and AUC_{VII}, respectively), calculated by the linear trapezoidal method.

Pharmacokinetic analysis

The pharmacokinetics of warfarin enantiomers were estimated using non-compartmental methods [24]. The elimination rate constant (k) was obtained by means of linear regression analysis, and the elimination half-life ($t_{1/2}$) was calculated by dividing ln2 by k. The area under the plasma concentration–time curve, during the initial dose of racemic warfarin ($AUC_{0\text{-}\infty}$) and over the dosing interval (AUC) and the area under the first moment of the plasma concentration–time curve ($AUMC_{0\text{-}\infty}$) were calculated using the linear trapezoidal rule; k was used to extrapolate the area from the last plasma concentration to infinity. Both apparent total clearance

Table 1 Average pharmacokinetic parameters of warfarin enantiomers estimated from data after the initial 15-mg oral dose of racemic warfarin

Pharmacokinetic parameter	*R*-Warfarin mean ± SD (range)	*S*-Warfarin mean ± SD (range)
$AUC_{0-\infty}$ (mg.h/l)	40.7 ± 10.3 (30.5–55.7)	28.2 ± 6.4 (22.0–39.2)
$t_{1/2}$ (h)	34.0 ± 5.0 (25.3–39.8)	26.9 ± 3.6 (21.2–31.3)
CL/F (ml/h)	194 ± 47.0 (134–246)	276 ± 56.3 (192–324)
V/F (l)	9.4 ± 2.0 (7.0–11.9)	10.6 ± 2.0 (8.6–13.2)
MRT (h)	51.3 ± 7.5 (38.1–59.0)	40.5 ± 5.5 (31.8–46.5)

(CL/F) and apparent volume of distribution (V/F) for the individual warfarin enantiomers were calculated from AUC data according to $CL/F = D/AUC_{0-\infty}$ and $V/F = (D/AUC_{0-\infty})/k$, where D is the dose of the individual warfarin enantiomer (50% of the racemic warfarin dose). Mean residence time (MRT) was calculated using the following equation: $MRT = AUMC_{0-\infty}/AUC_{0-\infty}$. The amounts of warfarin metabolites excreted into urine [Ae(m)] for the dosing interval were determined and expressed in warfarin equivalents. Apparent formation clearance values ($CL_{f,app}$) for the various metabolites were calculated according to $CL_{f,app} = CL_f fe(m) = Ae(m)/AUC$, where CL_f is the formation clearance, fe(m) is the fraction of the formed metabolite that is excreted unchanged into the urine and AUC is the area under the plasma concentration–time curve for the respective enantiomer of warfarin during the dosing interval.

Statistical analysis

Statistical analysis of data was made using the Student's *t*-test for paired data. Results are expressed as mean values ± SD or SEM. A *P* value of 0.05 or less was considered to be statistically significant.

Results

The mean (±SD) daily maintenance dose of racemic warfarin was 4.1 ± 1.6 mg/day and ranged from 2.5 mg to 6 mg. The mean values (±SD) of pharmacokinetic parameters for the two enantiomers of warfarin estimated from data after the initial 15-mg oral dose of racemic warfarin are summarised in Table 1. The pharmacokinetic parameter estimates were in agreement with those reported previously [17, 25].

The trough mean plasma concentrations for *R*- and *S*-warfarin are illustrated in Fig. 1. Trough plasma concentrations of warfarin enantiomers and their enantiomeric ratio (R/S), as well as trough prothrombin time and factor-VII clotting activity were compared between baseline and the end of cimetidine treatment (Table 2). Baseline values consisted of the mean of values determined on day 8 (just before cimetidine administration); end of cimetidine treatment values consisted of the mean values determined on day 15. Trough plasma concentrations of *S*-warfarin, the enantiomeric ratio (R/S) of plasma concentrations of warfarin enantiomers, and the trough prothrombin time and factor-VII clotting activity were essentially unchanged between baseline and end of cimetidine treatment. In contrast, *R*-warfarin trough plasma concentrations were significantly increased, by 28%, after the administration of cimetidine compared with baseline ($P < 0.05$).

Comparisons of apparent clearance values (dose/AUC) for the warfarin enantiomers and the AUC_{PT} and AUC_{VII} determined during the dosing interval at baseline (day 7) and at the end of cimetidine treatment (day 14) are presented in Table 3. Mean apparent clearance of *S*-warfarin and mean AUC_{PT} and AUC_{VII} values, which displayed marked variability, were not significantly affected by the concomitant administration of cimetidine. In contrast, co-administration of cimetidine with warfarin significantly decreased, by 23%, the

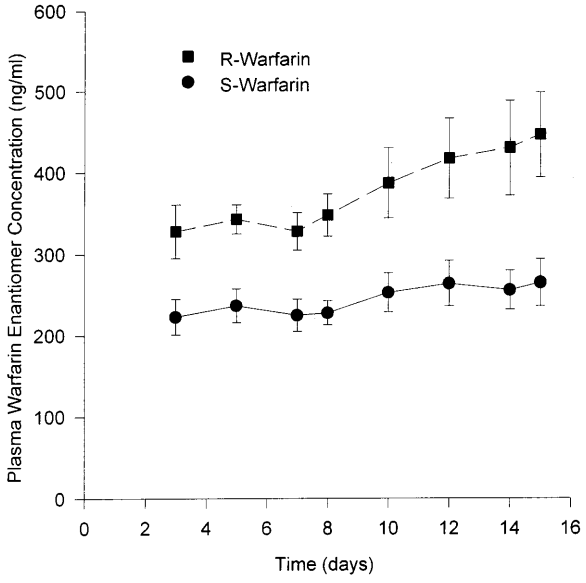

Fig. 1 Mean (±SEM) trough plasma concentrations of *R*- and *S*-warfarin during the study period. Volunteers received cimetidine from days 7–14. On day 7 and day 14, calculations of the area under the plasma concentration–time curves were performed

Table 2 Mean (±SEM) plasma concentrations of warfarin enantiomers, their enantiomeric ratio (R/S) and trough prothrombin-time and factor-VII clotting activity values for baseline (day 8) and at the end of cimetidine treatment (day 15)

Parameter	Baseline (day 8)	End of cimetidine treatment (day 15)
S-Warfarin trough plasma concentration (μg/ml)	0.228 ± 0.015	0.265 ± 0.029
R-Warfarin trough plasma concentration (μg/ml)	0.348 ± 0.026	0.446 ± 0.052*
Enantiomeric ratio (R/S)	1.54 ± 0.11	1.69 ± 0.10
Trough prothrombin time (s)	20.93 ± 1.60	21.08 ± 1.88
Trough factor-VII clotting activity (%)	64.42 ± 7.99	67.95 ± 7.59

*$P < 0.05$

Table 3 Mean (±SEM) apparent clearance values (CL/F) for the two enantiomers of warfarin and the mean areas under the prothrombin–time (AUC_{PT}) and factor-VII-clotting-activity–time (AUC_{VII}) curves as estimated at baseline (day 7) and at the end of cimetidine treatment (day 14)

Parameter	Baseline (day 7)	End of cimetidine treatment (day 14)
S-Warfarin CL/F (ml/h)	268 ± 21.5	246 ± 13.8
R-Warfarin CL/F (ml/h)	196 ± 8.31	151 ± 7.8*
AUC_{PT} (s.h)	491.7 ± 40.05	510 ± 46.4
AUC_{VII} (%.h)	1509.1 ± 180.4	1595.5 ± 202.5

*$P < 0.05$

R-warfarin apparent clearance (baseline 196 ± 44.8 vs cimetidine treatment 151 ± 19.1 ml/h; $P < 0.05$).

The urinary excretion of each warfarin metabolite expressed as a percentage of warfarin dose for the dosing interval (τ) during baseline (day 7) and at the end of cimetidine administration (day 14), is illustrated in Fig. 2. There was a significant decrease in the urinary excretion of both *R*-6-hydroxywarfarin ($P < 0.01$) and *R*-7-hydroxywarfarin ($P < 0.01$), whilst the urinary excretion of all other warfarin metabolites was not significantly affected following treatment with cimetidine. The $CL_{f,app}$ values for each warfarin metabolite determined for the dosing interval at baseline (day 7) and end of cimetidine treatment (day 14) are presented in Table 4. The $CL_{f,app}$ values for *R*-6-hydroxywarfarin and *R*-7-hydroxywarfarin were significantly decreased

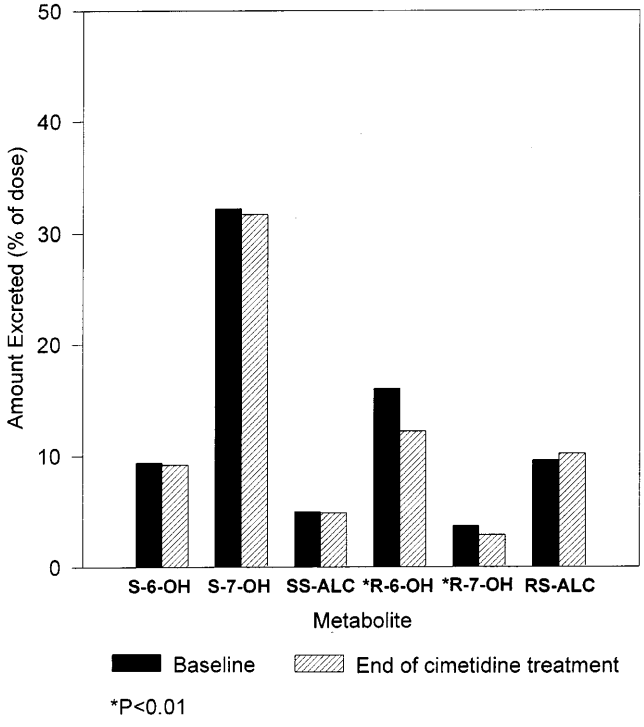

Fig. 2 Mean ± SD (% of dose) urinary recovery of warfarin metabolites over a 24-h period, determined during the dosing interval at baseline (day 7) and at the end of cimetidine treatment (day 14)

Table 4 Mean (±SD) estimated apparent formation clearance values ($CL_{f,app}$) of warfarin metabolites (ml/h) determined during the dosing interval at baseline (day 7) and at the end of cimetidine treatment (day 14)

Warfarin metabolite	Baseline (day 7)	End of cimetidine treatment (day 14)
S-Warfarin		
S-6-Hydroxywarfarin	25.3 ± 7.0	22.4 ± 4.0
S-7-Hydroxywarfarin	86.0 ± 16.7	77.7 ± 11.3
S,*S*-Warfarin alcohol	13.3 ± 3.2	11.9 ± 2.9
R-Warfarin		
R-6-Hydroxywarfarin	31.1 ± 7.4	18.5 ± 4.5*
R-7-Hydroxywarfarin	6.9 ± 1.3	4.3 ± 1.1*
R,*S*-Warfarin alcohol	18.8 ± 6.1	15.4 ± 2.5

*$P < 0.01$

by concurrent cimetidine treatment (31.1 ± 7.4 ml/h baseline; 18.5 ± 4.5 ml/h after cimetidine treatment; $P < 0.01$) and (6.9 ± 1.3 ml/h baseline; 4.3 ± 1.1 ml/h after cimetidine treatment; $P < 0.01$). Formation of all other metabolites was unaffected by cimetidine treatment.

Discussion

The pharmacokinetic parameter estimates of both enantiomers of warfarin after the initial 15-mg oral dose of racemic warfarin are consistent with those found previously [17, 25]. The more potent anticoagulant *S*-warfarin was eliminated faster than *R*-warfarin in agreement with previous findings [26, 27].

Both enantiomers of warfarin are eliminated almost entirely by metabolism in a stereoselective manner [17, 18, 28, 29]. The more pharmacologically potent *S*-warfarin is almost entirely oxidised primarily to form *S*-7-hydroxywarfarin and to a lesser extent *S*-6-hydroxywarfarin. In vitro investigations using cDNA-expressed human liver cytochrome P_{450} isoforms demonstrated that the formation of *S*-7-hydroxywarfarin and *S*-6-hydroxywarfarin is catalysed primarily by cytochrome CYP2C9 [12]. A small fraction of *S*-warfarin is stereospecifically reduced to *S*,*S*-warfarin alcohol. In contrast, the less-potent *R*-warfarin is almost equally metabolised by hydroxylation, to form mainly *R*-6-hydroxywarfarin and some *R*-7-hydroxywarfarin, and by stereospecific reduction to form *R*,*S*-warfarin alcohol. In vitro experiments indicate that the formation of *R*-6-hydroxywarfarin and *R*-7-hydroxywarfarin is mediated predominantly by CYP1A2 [12] and to a lesser extent through CYP2C19 [13]. The formation of *S*,*S*- and *R*,*S*-warfarin alcohols appears to be mediated by ketoreductases [30, 31].

Metabolite formation clearance values, CL_f, provide a useful measure of the efficiency of formation of an individual metabolite. In the estimation of formation clearance values, all the warfarin metabolites formed are assumed to be excreted unchanged in urine. In man, *R*,*S*- and *S*,*S*-warfarin alcohols are substantially excreted

unchanged [32] and conjugates of 6- and 7-hydroxylated metabolites have not been found in urine [27]. However, some of the hydroxylated metabolites appear in the faeces via biliary excretion [33], as the absorption of warfarin is assumed to be complete. Nonetheless, assuming that the values of fe(m) for each warfarin metabolite is high, the calculated CL_f values are minimal estimates, which are probably valid for comparison of the effect of cimetidine on warfarin metabolism. The values of CL_f determined for each warfarin metabolite at baseline are comparable with data reported previously [18, 25]. Warfarin is highly bound to albumin and, preferably, clearance should be estimated with respect to unbound drug. Cimetidine, however, does not alter the binding of warfarin [19]; thus, comparison based on total drug is a good measure of the effect of unbound drug.

Examination of the data in Table 5 show that concomitant cimetidine administration significantly inhibited the formation of *R*-6- and *R*-7-hydroxywarfarin. Cimetidine is known to be a non-selective inhibitor of cytochrome P_{450} isozymes, and it has been found to impair the hepatic oxidative metabolism of a wide variety of drugs [3, 4, 5, 6]. Although recognised as a general inhibitor, cimetidine does demonstrate some degree of specificity for individual cytochrome P_{450} isoforms, such as CYP2C19 [9]. Furthermore, in vitro cimetidine–warfarin interaction experiments using human liver microsomes indicated that cimetidine significantly decreased the formation of 6- and 7-hydroxylated metabolites of the less potent *R*-warfarin but not of the more potent *S*-warfarin [34]. Therefore, cimetidine impairs the oxidative metabolism of *R*-warfarin because it is an inhibitor of CYP1A2 and CYP2C19, which are responsible for the formation of *R*-6- and *R*-7-hydroxywarfarin. Thus, cimetidine, like enoxacin [17], omeprazole [35], ticlopidine [36] and zileuton [37], interacts stereoselectively decreasing the clearance of the less potent *R*-warfarin.

Both trough prothrombin time and factor-VII clotting activity, and AUC_{PT} and AUC_{VII} estimated at baseline and at the end of cimetidine treatment were used as measures of anticoagulation. Although overall anticoagulant response was not significantly affected after cimetidine treatment, there were potentially clinically significant changes in anticoagulant response in some subjects. Large variability in anticoagulant response was noted, however, amongst the subjects. In three of these subjects, concomitant administration of cimetidine increased trough prothrombin time and AUC_{PT} by 10% or more and decreased trough factor-VII clotting activity and AUC_{VII} by 10% or more relative to baseline. Potential explanations for these findings may be related, in part, to the intra- and inter-subject variability in the pharmacodynamics of warfarin viewed in terms of prothrombin time or factor-VII clotting activity [16, 17, 23]. As with enoxacin, omeprazole and ticlopidine, the anticoagulant response was not significantly affected in the group of six young male volunteers studied after cimetidine treatment, although considerable inter-subject variability was noted. Therefore, it is possible that other individuals exist who may show a clinically significant cimetidine–warfarin interaction.

In conclusion, cimetidine significantly reduced the clearance of the less-potent anticoagulant *R*-enantiomer of warfarin by inhibiting CYP1A2 and CYP2C19 enzymes responsible for the formation of both *R*-6- and *R*-7-hydroxywarfarin. As with many warfarin interactions, large variability in the hypoprothrombinemic response was noted from one subject to another. Therefore, co-administration of cimetidine with warfarin may produce a potentially clinically significant increase in the anticoagulant response in some patients.

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