Br. J. clin. Pharmac. (1992), **34**, 509–512

A study of the interaction of omeprazole and warfarin in anticoagulated patients

P. UNGE, L.-E. SVEDBERG[1], A. NORDGREN, H. BLOM[1], T. ANDERSSON[2], P.-O. LAGERSTRÖM[3] & J.-P. IDSTRÖM

Department of Medicine, Sandviken Hospital, Sandviken, [1]Department of Medicine, Bollnäs Hospital, Bollnäs, [2]Clinical Pharmacology and [3]Bioanalytical Chemistry, Astra Hässle AB, Mölndal, Sweden

1 Thirty-five patients on continuous therapy with warfarin were given omeprazole 20 mg once daily and placebo each for 3 weeks according to a two-centre randomised double-blind cross-over design.

2 Blood samples were obtained once weekly during the run-in and follow-up periods as well as during the first 2 weeks of each treatment period, and twice during the last week of each treatment period. Plasma concentrations of R- and S-warfarin were measured by h.p.l.c. and the anticoagulant effect was assessed using the Trombotest®.

3 Twenty-eight patients were evaluated. The mean plasma concentration of R-warfarin was increased by 9.5% during omeprazole treatment compared with placebo, while that of S-warfarin, the more active isomer, was unaffected. The coagulation time was not significantly changed (106 s during omeprazole and 98 s during placebo). Corresponding TT-values (Trombotest®) were 8.8 and 9.9 (NS).

Keywords omeprazole warfarin interaction patients anticoagulation

Introduction

Omeprazole suppresses gastric secretion by inhibiting the H^+, K^+, ATPase (acid pump) in the parietal cell (Fellenius *et al.*, 1981; Wallmark *et al.*, 1984). It has been shown to be completely metabolised by the cytochrome P450 system in the liver, largely by S-mephenytoin hydroxylase (Andersson *et al.*, 1990a). Diazepam is also metabolised by this enzyme and, accordingly, a decreased clearance of this drug after omeprazole treatment has been reported (Andersson *et al.*, 1990b; Bertilsson *et al.*, 1989). However, the metabolism of several other drugs metabolised by other P450 isoenzymes is unaltered by omeprazole treatment suggesting that omeprazole may only influence the metabolism of the limited number of drugs shown to be metabolised by S-mephenytoin hydroxylase (Andersson, 1991).

The metabolism of the anticoagulant warfarin, which is mediated by several P450 isoenzymes (Wang *et al.*, 1983), has been shown in healthy volunteers to be slightly impaired by omeprazole treatment (Sutfin *et al.*, 1989). However, only plasma concentrations of the R-isomer of warfarin were increased (12%), while those of the 5 times more potent S-isomer were unaltered. The present study was performed to determine whether this effect might be of clinical significance in patients on continuous anticoagulant therapy with warfarin.

Methods

Thirty-five patients (35–72 years of age) on continuous and stable anticoagulant therapy with warfarin were included in this study, which was conducted in accordance with the 'Declaration of Helsinki'. The study was approved by the Ethics Committee of the University of Uppsala, Sweden, and by the Swedish National Board of Health and Welfare. Written informed consent was obtained from each patient prior to participation in the study.

The study was conducted as a randomised double-blind cross-over trial. Patients already stabilised on warfarin also received omeprazole and placebo, respectively, once daily for 3 consecutive weeks each. Blood samples for the measurement of coagulation time and plasma concentrations of the two warfarin enantiomers (R and S) were taken before, during and after the omeprazole/placebo treatments.

The warfarin dose was adjusted to stabilise the patients at a coagulation time corresponding to a TT-value (determined by Trombotest®) between 5 and 18. The warfarin dose was kept constant during the whole study, except in cases where it was judged clinically necessary to change it. Omeprazole 20 mg was given as commercially available enteric coated granules dispensed in hard gelatin capsules. Sugar granules in capsules identical to those of

Correspondence: Dr Tommy Andersson, Clinical Pharmacology, Astra Hässle AB, S-431 83 Mölndal, Sweden

omeprazole, were provided for the placebo. One capsule was taken daily before breakfast. Half of the patients were allocated to omeprazole treatment followed by placebo treatment and in the others the treatment order was reversed. Alcohol intake was minimised and kept constant during the study, as well as smoking.

Blood samples (5 + 6 ml) were taken on the morning of the first day in each week during the 2 weeks run-in and during the two treatment periods of 3 weeks each. Additional blood samples were taken on the morning of the last two days in each treatment period, and these samples were used for statistical evaluation of the potential effect of omeprazole on coagulation time and plasma concentrations of warfarin enantiomers. Furthermore, one blood sample was taken on the morning of the last day in each of the two follow-up weeks. Blood and urine samples were collected at the pretreatment examination and at the end of each treatment period for routine clinical screening.

The blood was taken by separate venepuncture from a forearm vein. Whole blood (5 ml) was collected in a citrated tube for assessment of three of the vitamin K-dependent coagulation factors (II, VII, X). The citrated plasma was separated and analysed in the Departments of Clinical Chemistry, Sandviken and Bollnäs Hospitals by the Trombotest®. Whole blood (6 ml) was collected in a heparinised tube for the assay of plasma concentrations of the warfarin enantiomers. The plasma was separated and stored at −20° C until analysis. The warfarin isomers together with the internal standard chlorowarfarin were extracted from plasma into hexane/dichloromethane (1:5, v/v). The extract was evaporated to dryness, redissolved in mobile phase and injected onto a Chiralcel OC column. The compounds were separated and measured with a fluorescence detector operated at 315/370 nm. The mobile phase used contained acetonitrile-1-propanol-hexane (2:15:83). The lower limit of quantitation (CV < 10–15%) was 100 nmol l^{-1} of each enantiomer. The analyses were performed at Bioanalytical Chemistry, Astra Hässle AB, Mölndal, Sweden (Lagerström, Andersen & Balmér, to be published).

The following variables were analysed: blood coagulation factor (TT-value), blood coagulation time obtained in the TT-test (s), and plasma concentration of R- and S-enantiomers. The distributions of the variables were assumed to be lognormal and values were transformed accordingly before statistical analyses. A 95% confidence interval for the estimated mean effect was calculated for each variable. The effect was defined as the geometric mean of the absolute measurements at the two last visits (blood samples) for each period. The reason for choosing the last two data points was that steady-state was not expected until after 2 week's treatment. The treatments were compared in terms of the 95% confidence interval for the ratio (omeprazole/placebo) of the estimated mean effects. If an interval contained the digit 1 there was no significant difference at the 5% level.

The period and carry-over effects in the study were tested according to the methods described by Pocock (1983).

Results

Seven patients were excluded prior to evaluation for the following reasons; 1—alcohol abuse during the study, 1—high TT-values in run-in period, 1—diarrhoea for 1 week during one of the treatment periods, 1—change in concomitant medication, 1—change in warfarin dose during the placebo period, 2—non-compliance with warfarin dosing. Data from twenty-eight patients were analysed according to protocol. No period or carry-over effects were observed. There were no changes in warfarin or other drug dosage during the two study periods, and no serious adverse event was reported during administration of omeprazole.

The geometric means of R- and S-warfarin plasma concentrations over the entire study period for the two sequence groups are illustrated in Figure 1. Each data point in the omeprazole/placebo sequence represents the mean of 13 patients and each point in the placebo/omeprazole sequence represents the mean of 15 patients. Corresponding values for coagulation status (TT-values) are shown in Figure 2. Mean values of plasma R- and S-warfarin for the omeprazole and placebo treatment together with the ratio between treatments are shown in Table 1, and corresponding figures for the TT-values and time in seconds are presented in Table 2.

The mean plasma concentration of R-warfarin was increased by 9.5% during omeprazole treatment compared with placebo, while that of S-warfarin was

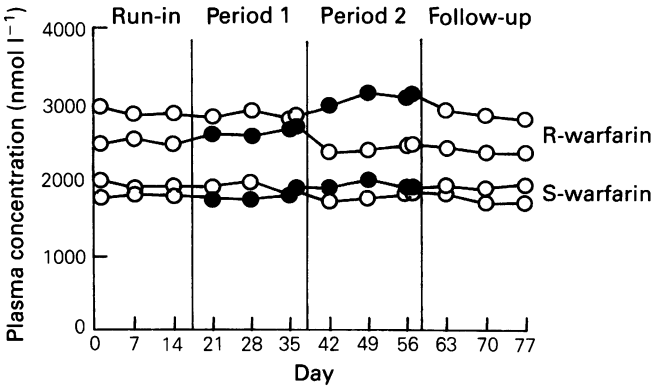

Figure 1 Plasma concentrations of R- and S-warfarin (nmol l^{-1}) during omeprazole, 20 mg once daily (filled), and placebo treatment, presented in chronological sequences; n = 13 for omeprazole/placebo, n = 15 for placebo/omeprazole.

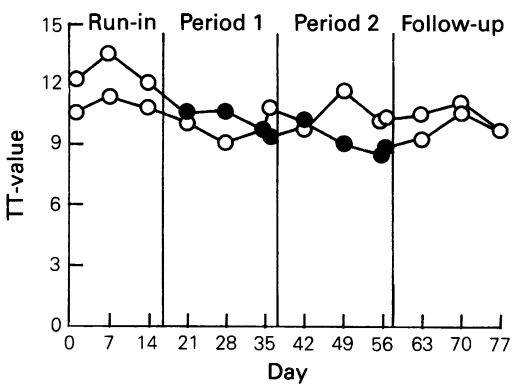

Figure 2 TT-values during omeprazole, 20 mg once daily (filled), and placebo treatment, presented in chronological sequences; n = 13 for omeprazole/placebo, n = 15 for placebo/omeprazole.

unaffected. The coagulation time was not changed significantly as assessed by the Trombotest®, mean TT-values were 8.8 and 9.9 during the omeprazole and placebo periods, respectively. The individual changes are shown in Figure 3. Corresponding values expressed in seconds were 106 and 98.

Table 1 Geometric mean values and 95% confidence intervals for the plasma concentrations (nmol l^{-1}) of R- and S-warfarin during omeprazole and placebo treatment together with the ratio of values between treatments (omeprazole/placebo) and corresponding *P* value; $n = 28$

Enantiomer	*Treatment*	*Mean*	*95% confidence interval*	P *value*
R-warfarin	Omeprazole	2691	2273–3186	
	Placebo	2457	2085–2897	
	Ratio (ome/pla)	1.095	1.044–1.149	< 0.05
S-warfarin	Omeprazole	1728	1465–2038	
	Placebo	1705	1448–2008	
	Ratio (ome/pla)	1.013	0.963–1.065	0.60

Table 2 Geometric mean values and 95% confidence intervals for the coagulation time (expressed as TT-values or seconds) during omeprazole and placebo treatment together with the ratio between treatments (omeprazole/placebo) and corresponding *P* value; $n = 28$

Coagulation time	*Treatment*	*Mean*	*95% confidence interval*	P *value*
TT-value	Omeprazole	8.85	7.99–9.81	
	Placebo	9.92	9.00–10.92	
	Ratio (ome/pla)	0.893	0.793–1.005	0.06
Seconds	Omeprazole	106	99–114	
	Placebo	98	92–105	
	Ratio (ome/pla)	1.082	0.996–1.176	0.06

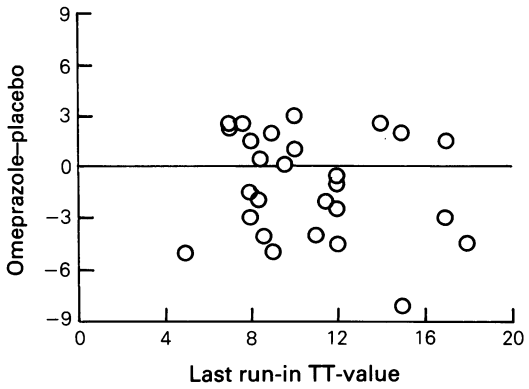

Figure 3 Change in TT-value between the omeprazole and placebo treatments (omeprazole-placebo) in relation to last run-in value; $n = 28$.

Discussion

The results show that plasma concentrations of R-warfarin, but not those of the more potent S-isomer, are slightly elevated during omeprazole treatment. This has no significant influence on the coagulation time as assessed by Trombotest®, although the *P*-value of 0.06 indicated that it was close to the level of significance. These results are in good agreement with those previously found in healthy volunteers (Sutfin *et al.*, 1989), except for a small but statistically significant effect on coagulation time (TT-values decreased from 21 to 19 in the volunteers). However, Sutfin *et al.* (1989) noted that those volunteers with TT-values nearest to the therapeutic range (5 to 15%) exhibited less change during omeprazole treatment compared with those with higher values. Thus, patients on continuous warfarin therapy exhibiting an anticoagulant effect within the therapeutic range may be less prone to alteration in this effect by omeprazole treatment.

The effect of omeprazole on the plasma concentrations of R-warfarin is probably due to an interaction at the enzyme level resulting in a stereoselective inhibition of the hepatic metabolism of this enantiomer. The enantiomers of warfarin are metabolised to different hydroxy products with different enzyme selectivity (Kaminsky, 1989; Wang *et al.*, 1983). It is known that omeprazole is metabolised by S-mephenytoin hydroxylase and consequently has the potential to inhibit the metabolism of other drugs which are substrates of the same enzyme (Andersson, 1991; Andersson *et al.*, 1990a). S-mephenytoin hydroxylase belongs to the same subfamily of enzymes as tolbutamide hydroxylase (Relling *et al.*, 1990). Tolbutamide hydroxylase has recently been shown also to metabolise phenytoin (Veronese *et al.*, 1991) and, except for diazepam which is a substrate for S-mephenytoin hydroxylase, the only other drug which has been shown to interact metabolically with omeprazole is phenytoin. Therefore, omeprazole appears to be a partial inhibitor of enzymes within this subfamily of enzymes, P4502C, and the most probable explanation of the interaction of omeprazole with R-warfarin is that at least one of the metabolic reactions of R-warfarin is mediated by a 2C isoenzyme.

We conclude that omeprazole treatment, 20 mg once daily, results in slightly elevated plasma concentrations of R-warfarin, while those of the more potent S-enantiomer are not affected. This is not accompanied by a significant effect on coagulation time in patients on continuous warfarin therapy.

References

Andersson, T. (1991). Omeprazole drug interaction studies. *Clin. Pharmacokin.*, **21**, 195–212.

Andersson, T., Regårdh, C. G., Dahl-Puustinen, M. L. & Bertilsson, L. (1990a). Slow omeprazole metabolizers are also poor S-mephenytoin hydroxylators. *Ther. Drug Monit.*, **12**, 415–416.

Andersson, T., Cederberg, C., Edvardsson, G., Heggelund, A. & Lundborg, P. (1990b). Effect of omeprazole treatment

on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. *Clin. Pharmac. Ther.*, **47**, 79–85.

Bertilsson, L., Henthorn, T. K., Sanz, E., Tybring, G., Säwe, J. & Villén, T. (1989). Importance of genetic factors in the regulation of diazepam metabolism: Relationship to S-mephenytoin, but not debrisoquine, hydroxylation phenotype. *Clin. Pharmac. Ther.*, **45**, 348–355.

Fellenius, E., Berglindh, T., Sachs, G., Olbe, L., Elander, B., Sjöstrand, S. E. & Wallmark, B. (1981). Substituted benzimidazoles inhibit gastric acid secretion by blocking (H^+,K^+)-ATPase. *Nature*, **290**, 159–161.

Kaminsky, L. S. (1989). Warfarin as a probe of cytochromes P-450 function. *Drug Metab. Rev.*, **20**, 479–487.

Pocock, S. (1983). *Clinical trials*, pp. 116–117. Chichester, England: Wiley and Sons.

Relling, M. V., Aoyama, T., Gonzalez, F. J. & Meyer, U. A. (1990). Tolbutamide and mephenytoin hydroxylation by cytochrome P450s in the CYP2C subfamily. *J. Pharmac. exp. Ther.*, **252**, 442–447.

Sutfin, T., Balmér, K., Boström, H., Eriksson, S., Höglund, P. & Paulsen, O. (1989). Stereoselective interaction of omeprazole with warfarin in healthy men. *Ther. Drug. Monit.*, **11**, 176–184.

Wallmark, B., Brändström, A. & Larsson, H. (1984). Evidence for acid-induced transformation of omeprazole into an active inhibitor of (H^+,K^+)-ATPase within the parietal cell. *Biochim. Biophys. Acta*, **778**, 549–558.

Wang, P. P., Beaune, P., Kaminsky, L. S., Dannan, G. A., Kadlubar, F. F., Larrey, D. & Guengerich, F. P. (1983). Purification and characterisation of six cytochrome P-450 isozymes from human liver microsomes. *Biochemistry*, **22**, 5375–5383.

Veronese, M. E., Mackenzie, P. I., Doecke, C. J., McManus, M. E., Miners, J. O. & Birkett, D. J. (1991). Tolbutamide and phenytoin hydroxylation by cDNA-expressed human liver cytochrome P4502C9. *Biochem. Biophys. Res. Comm.*, **175**, 1112–1118.

(*Received 23 December 1991, accepted 15 May 1992*)