A PHARMACOKINETIC INTERACTION STUDY BETWEEN OMEPRAZOLE AND THE H_2-RECEPTOR ANTAGONIST RANITIDINE

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SUMMARY

The effect of ranitidine pretreatment on the pharmacokinetics of omeprazole was investigated in 14 male human volunteers. Omeprazole (40 mg, gastroresistant pellets) was administered to the volunteers in a two-treatment study design, either alone or after 5 days pretreatment with b.i.d. doses of 150 mg ranitidine. Plasma concentrations of omeprazole were determined over a 24-hour period following drug administration, by a validated RP-HPLC method. Pharmacokinetic parameters were calculated with compartmental and non-compartmental analysis, using the computer program Kinetica (Inna Phase). In the two periods of treatments, the mean peak plasma concentrations C_{max} were 730.8 ng/ml for omeprazole alone and 802.1 ng/ml for omeprazole co-administered with ranitidine (not significant). The time taken to reach the peak, T_{max}, was 1.29 h and 1.42 h, respectively (not significant). The areas under the curve (AUC_{0-10}) were 1,453.3 ng.h/ml and 1,736.8 ng.h/ml for the two periods of treatment; thus a greater AUC was obtained after pretreatment with multiple doses of ranitidine. Our data show that the pharmacokinetics of omeprazole might be inhibited by pretreatment with ranitidine; however, the clinical relevance of this interaction still has to be confirmed.

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KEY WORDS

omeprazole, ranitidine, pharmacokinetics, interaction

INTRODUCTION

The proton pump inhibiting class of acid-suppressing drugs has been a valuable tool in the treatment of a range of upper gastrointestinal diseases. Omeprazole, a selective H^+/K^+ ATPase inhibitor in the gastric parietal cell, is widely used in various gastric acid-related disorders. The bioavailability of omeprazole is 35% after the first dose, and it increases to about 60% with repeated doses. One potential reason for these characteristics is that the metabolism of omeprazole may be saturated over time, which then results in increased serum concentrations and is indicative of non-linear pharmacokinetics.

Because of its acid lability, omeprazole is available as a delayed-release capsule containing enteric-coated granules. Plasma concentrations increase over the first several days of therapy, suggesting that acid suppression increases bioavailability /1-4/.

Omeprazole is metabolized by the CYP system, primarily CYP2C9 and 2C19, but also CYP3A, thus there is the potential for interaction with other drugs. In high concentrations omeprazole induces CYP1A2. Similar to antacids and H_2-receptor antagonists, it may alter the bioavailability of other drugs /5/. Omeprazole is also an inhibiting agent. Omeprazole increases concentrations of phenytoin, diazepam, *R*- and *S*-isomers of warfarin, and tacrolimus /6/.

Pharmacological options for the management of gastro-esophageal reflux disease via the mechanism of antisecretory therapy include not only proton pump inhibitors, but also histamine H_2-receptor antagonists (cimetidine, ranitidine) /7/.

Some potential drug-drug interactions can be predicted by identification of the isozyme that metabolizes the drugs in question. Omeprazole is a substrate of and is metabolized by CYP2C9, and binding of ranitidine may inhibit its metabolism to the same isozyme. Cimetidine and other histamine H_2-receptor antagonists inhibit CYP2C19 and CYP2C9, but ranitidine is a weak inhibitor. Cimetidine and ranitidine have been shown to influence the bioavailability of a number of orally administered drugs by increasing the intragastric pH /6-9/.

The aim of the present study was to determine whether or not ranitidine has any effect on the pharmacokinetics of omeprazole, after repeated administration of ranitidine, in a group of healthy volunteers.

MATERIALS AND METHODS

Chemicals

Omeprazole 20 mg capsules (Omeran®) was obtained from GSK& Europharm, Brasov, Romania; ranitidine 150 mg capsules (Ranitidin®) from A.C. Helcor, Baia-Mare, Romania; acetonitrile was HPLC grade (Merck, Germany); all other chemicals used were AR grade.

Subjects

Fourteen healthy, non-smoking young males, mean age 22.4 ± 3.8 years (range 21-29 years), mean height 182.4 ± 3.0 cm (160-187 cm), and mean weight 65.6 ± 5.6 kg (56-75 kg) participated in this study, which was approved by the University of Medicine and Pharmacy of Cluj-Napoca Ethics Committee. All volunteers gave their written informed consent prior to inclusion. The volunteers were healthy according to history, physical examination and laboratory tests, had no history of alcohol or drug abuse, and did not take any regular medication.

Study design

The study consisted of two periods: Period 1 (reference), when each volunteer received a single dose of 40 mg omeprazole (as two capsules of 20 mg) and Period 2 (test), when each volunteer received a single dose of 40 mg omeprazole (as two capsules of 20 mg) and 150 mg ranitidine; the two treatment periods were separated by 5 days of multiple dose administration of 150 mg ranitidine twice a day. After an overnight fast (12 h) each volunteer received the omeprazole dose with 150 ml of water.

Venous blood (5 ml) was drawn into heparinized tubes, on the first and the last day of the study, before drug administration as well as at 0.5, 1, 1.33, 1.66, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours after drug administration, and the separated plasma was stored frozen (-20°C) until analysis.

Sample assays

Omeprazole plasma concentrations were determined by a validated RP-HPLC method with UV detection. The HPLC system was a HP 1100 series (binary pump, autosampler, thermostat, UV detector). It utilized a Zorbax SB-C18 column (75 mm x 4.6 mm i.d., 3.5 μm), a mobile phase containing 33:67 (v/v) acetonitrile:30 mM K_2HPO_4 buffer, pH 6.5 with H_3PO_4. The flow rate was 1.5 ml/min and the thermostat temperature set at 35°C. UV detection was at 303 nm.

To 0.5 ml plasma, 6 ml mixture dichlormethan/diethyl ether was added in a centrifuge tube. The tube was capped and shaken for 10 min on a vortex mixer. After centrifugation and separation, the organic layer was evaporated at 30°C. The residue was dissolved in 200 μl Na_2HPO_4 0.1 M, and finally 50 μl was injected onto the chromatographic system.

The calibration curve was linear in the range 7.7-772 ng/ml plasma, with correlation coefficient r = 0.9997. At quantification limit, accuracy and precision were 8.2% and 11.2% (intra-day), and 10.2% and 11.7% (inter-day), respectively.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters of omeprazole were calculated using standard equations /10,11/. The area under the plasma concentrations versus time curve ($AUC_{t(0-10)}$) was determined by linear trapezoidal rule and $AUC_{i(0-\infty)}$ was obtained from the equation:

$$AUC_{(0-\infty)} = AUC_{(0-t)} + C_{last} / K_{el}$$

where C_{last} is the last measured concentration and K_{el} is the first-order, terminal elimination rate constant. The value of the half-life was calculated by the equation: $t_{½} = 0.693/K_{el}$.

Peak plasma concentration (C_{max}) and the time to reach peak (T_{max}) were obtained from the plasma concentration data of each volunteer.

In order to evaluate the statistical difference between pharmacokinetic parameters the ANOVA test and the procedure recommended in bioequivalence studies was followed /12,13/. The analysis of variance (ANOVA) was completed by the assessment of the value of the ratio between the mean values of the AUC_t, AUC_i and C_{max}, as well as of the 90% confidence interval for the ratio of log mean values of tested and reference treatment. The 90% confidence interval was

calculated for the bioequivalence domain (0.80-1.25), using the one-sided double t-test (Schuirman test), for the ratio test/reference of the mean logarithmic values of the pharmacokinetic parameters AUC and C_{max} /14/. In the case of T_{max}, the difference between the mean values was used to assess the statistical significance of the differences by using the non-parametric Friedman test.

Pharmacokinetic and statistical calculations were made with the Kinetica 4.02 program (Inna Phase, USA).

RESULTS

The mean plasma concentrations of omeprazole when administered alone or in combination with ranitidine (after 5 days treatment with twice a day 150 mg ranitidine) are shown in Figure 1. Pharmacokinetic parameters are presented in Table 1.

Peak plasma concentrations (C_{max}) of omeprazole before and after the ranitidine multiple doses of treatment (730.8 ng/ml vs 802.11

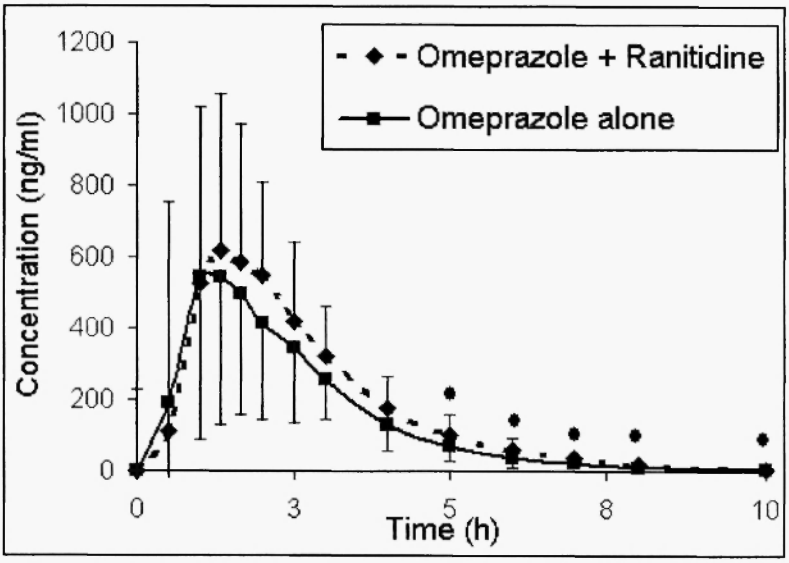

Fig. 1: Mean (± SD) plasma levels of omeprazole (2x20 mg p.o.) when given alone or in combination with ranitidine (150 mg p.o.) after multiple doses of ranitidine for 5 days (2x150 mg p.o. b.i.d.) (n = 14). * $p < 0.05$.

TABLE 1

Pharmacokinetic parameters (mean ± SD) of omeprazole (40 mg) in human volunteers (n = 14) before and after pretreatment with ranitidine (150 mg b.i.d. x 5) and statistical analysis

	Omeprazole alone	**Omeprazole + ranitidine** (after ranitidine twice daily for 5 days)	**90% CI** (Schuirman test)
C_{max} (ng/ml)	730.8 ± 429.98	802.11 ± 483.65	0.94899-1.2689**
$AUC_{t(0-10)}$ (ng.h/ml)	1,453.3 ±1,151.5*	1,736.8 ±1,409.68	1.0639-1.3175**
$AUC_{i(0-\infty)}$ (ng.h/ml)	1,465.9 ±1,158.28	1,758.2 ±1,426.4*	1.067-1.3226**
T_{max} (h)	1.29±0.54	1.42±0.51	$CHI^2 = 3.841$. (Friedman, NS)
$t_{½}$ (h)	1.13 ± 0.54	1.21 ± 0.42	NS

* $p < 0.05$, test vs reference.
** Cannot conclude equivalence.
NS = not significant.

ng/ml) did not differ significantly between the two different treatments, nor did the time to attain peak plasma concentrations (T_{max}) (1.29 h vs 1.42 h) and the terminal half-life ($t_{½}$) (1.13 h vs 1.21 h) (Table 1).

The difference in AUC of omeprazole between the two treatments until the last sampling time, AUC_t, (1,453.3 ng.h/ml vs 1,736.8 ng.h/ml) and at infinity, AUC_i, (1,465.9 ng.h/ml vs 1,758.2 ng.h/ml) are statistically significant (Table 1).

The Schuirman test showed that the 90% confidence interval for the ratio of the mean logarithmic values of AUC_t, AUC_i and C_{max} of the test and reference treatments was not in the domain of equivalence of 0.8-1.25, in other words there are significant differences of these parameters in the two treatments. However no statistical differences were observed for the half-life, i.e. the rate constant of elimination

(Table 1). In the case of T_{max}, the Friedman test showed no statistical differences between the two treatments.

DISCUSSION

This study describes the effect of ranitidine pretreatment on the pharmacokinetics of omeprazole in healthy male human volunteers. The present study showed that b.i.d. treatment with 150 mg ranitidine for 5 days (co-treatment with ranitidine) has an influence on the pharmacokinetics of a single oral dose of omeprazole. This implies that there is a possibility of an interaction between the two drugs in the absorption, metabolism or excretion phases.

The fact that the T_{max} value of omeprazole was not significantly altered by ranitidine indicates that absorption might not be affected. The H_2-receptor antagonist may cause a rise in the pH of the gastric content, but is not sufficient to produce liberation of the omeprazole from gastroresistant pellets whose coated polymer dissolves only at a pH greater than 6.5.

The value of the difference in the mean values of the half-life were not statistically different, proving the lack of difference in the elimination of the omeprazole in the two treatments.

The increase in omeprazole bioavailability after multiple doses of ranitidine may have an explanation in a metabolic interaction due to inhibition of the metabolism of the omeprazole by the pretreatment with ranitidine, because the AUC is greater after ranitidine pretreatment.

Omeprazole metabolism in man is mediated through CYP2C9 and the metabolism of a number of compounds via this pathway has been shown to be inhibited by cimetidine and ranitidine /15/. Like cimetidine, ranitidine binds to CYP450 in the liver where it appears to exert an inhibitory effect, but to a lesser extent than cimetidine. Both these H_2-receptor antagonists may also reduce hepatic blood flow. Several interactions between ranitidine and other drugs have been established, which may be attributed variously to an effect of ranitidine on hepatic metabolism (warfarin, metoprolol, nifedipine, theophylline, fentanyl) or to an effect on the absorption of concomitantly administered drugs (midazolam, procainamide). However, some of these pharmacokinetic interactions appear unlikely to be of clinical significance /15/.

Based on literature reports, we also expect a possible role of decreased expression of CYP450 enzymes by ranitidine pretreatment, resulting in the decreased metabolism of omeprazole.

In clinical practice, omeprazole may be co-administered or administered after pretreatment with drugs that inhibit CYP2C9, such as ranitidine. Our data showed that the pharmacokinetics of omeprazole might be inhibited by pretreatment with ranitidine; however, the clinical relevance of this interaction still has to be confirmed.

CONCLUSIONS

Pretreatment with ranitidine until steady state plasma concentration has been reached has an influence on the pharmacokinetics of a single oral dose of omeprazole in young healthy volunteers. Our data showed that the pharmacokinetics of omeprazole might be inhibited by pretreatment with ranitidine; however, the clinical relevance of this interaction still has to be confirmed.

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