PLASMA CONCENTRATION-TIME PROFILE OF A SINGLE DOSE OF ENTERIC-COATED OMEPRAZOLE IN MALE AND FEMALE HEALTHY VOLUNTEERS

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ABSTRACT

Objective: The bioavailability of a single dose (20 mg) of two enteric-coated omeprazole formulations, marketed in Turkey, given 10-15 min before breakfast, was studied in 12 healthy volunteers (6 males and 6 females) in a double-blind, crossover design.

Methods: Blood samples were collected prior to and at 10 time points within 12 hrs. after dosing. Plasma omeprazole concentrations were measured by HPLC technique in our laboratory.

Results and Conclusions: The two products were found to be bioequivalent in terms of extent of absorption (the area under the plasma concentration-time curves). Multipeak plasma concentration profiles were seen in most of the subjects with both products. Time to the earlier peaks was 1-2 hrs. and those peaks were lower in amplitude than the peaks reached approximately 4.5 hrs. after the application. Interestingly, the multipeak profile was more frequent and the earlier peaks were significantly higher in female subjects than in males. The reason for this gender difference in multipeak plasma concentration - time profile of oral omeprazole needs further investigation.

Key Words: Omeprazole - Bioavailability - Enteric - coated capsules - Gender difference

INTRODUCTION

Omeprazole, a substituted benzimidazole derivative causes the potent and long-lasting inhibition of gastric acid secretion by selectively interacting with the gastric proton pump (H^+-K^+-ATPase) in the parietal cell secretory membrane (1-3). The degree of gastric acid suppression is correlated with the area under the plasma omeprazole concentration-time curve (AUC) and not directly related to the plasma concentration of the drug at any given time (4). The long lasting effect of omeprazole on the H^+-K^+-ATPase in the parietal cells, despite its short plasma half life, accounts for the lack of correlation between plasma concentration and degree of acid inhibition (2).

Since omeprazole is acid labile, acid-resistant enteric-coated granules or capsules have been developed. Although the extent of absorption was reported not to be influenced by the presence of food in the stomach, multipeak or single-peak plasma concentration-time profiles were found after the oral administration of omeprazole administered before and after

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breakfast, respectively. The present study was planned to investigate the bioavailability and plasma concentration-time profiles after a single oral dose of two omeprazole formulations marketed in Turkey in male and female healthy volunteers. Both preparations are in delayed release, enteric-coated, capsule forms.

MATERIAL AND METHOD

Subjects: Twelve healthy adult volunteers (6 females, 6 males) aged between 20-26 years, weighing 49-87 kg were included in the study. The subjects were assessed by a medical history, physical examination, biochemical investigations for kidney and liver functions and hematological examinations; the values and findings were within the normal limits. None of the subjects received any other medication for 4 weeks prior to the study and during the study period. The study was conducted in accordance with the Declaration of Helsinki. A fully informed written consent was obtained from each volunteer. The study was approved by the Ethics Committee of Marmara University, School of Medicine.

Study design: A randomized, double blind, crossover design with a washout period of 7 days between the treatments was used. Each subject received one capsule of either product "A" or "B" (20 mg omeprazole) at 8:00-9:00 a.m. one week apart. A standard breakfast was given 10-15 minutes after the drug administration to all the volunteers. Calorie intake and physical exercise were also standardized during the study period.

Blood samples (5 ml each) were collected by venipuncture from the forearm at 0,1,2,2.5,3,3.5,4,5,6,8 and 12 hrs. after the drug administration.The plasma was separated immediately by centrifugation at 3000 rpm for 10 minutes and was buffered by adding 4 µl of 1.0 M sodium carbonate per ml of plasma. The samples were stored at - 70°C until assayed for omeprazole.

Analysis: Plasma omeprazole concentrations were measured by high performance liquid chromatography (HPLC) technique of Kobayashi et al.(5). The HPLC system consisted of a pump (Jasco, PU980), a UV detector with variable wavelength (Jasco, UV975), a Rheodyne valve (R7725) as an injection unit, a computing integrator (Calibra 386 PC), and a reversed phase C18 column packed with Nucleosil 100 (length 25 cm, internal diameter 4 mm, particle size 5 µm; Macherey-Nagel). The mobile phase was acetonitrile-0.05 M phosphate buffer (pH=8.5; 30:70 v/v) and the mixture was filtered and degassed before use. Separations were made at ambient temperature with a flow rate of 1.0 ml/min. Detection was performed at a wave length of 302 nm.

Statistics: The linearity of the assay was examined for omeprazole at concentrations ranging from 30-1000 ng/ml in plasma. Standard samples were prepared by adding the analyte to drug-free plasma and were extracted as described by Kobayashi et al. (5). Peak areas were measured and the calibration graph was obtained from the least-squares linear regression. The regression line was used to calculate the concentrations of the respective analytes in the unknown samples. The intra- and interassay coefficients of variation (C.V.) were <20%. The peak plasma concentration (C_{max}) and the time to reach peak plasma concentration (t_{max}) were calculated from the actual observed plasma data of each volunteer. The area under the plasma omeprazole concentration-time curve (AUC_{0-t}) by trapezoidal rule and the $AUC_{t-\infty}$ by dividing the last observed omeprazole concentration by elimination rate constant. The data are expressed as mean±S.E.M. and were analyzed statistically by the Student's paired t-test.

RESULTS

All the subjects completed the study and no adverse events were observed. The individual plasma concentration-time profiles after the administration of enteric-coated omeprazole capsules showed interindividual variation with both preparations. In some cases, a single peak was observed, whereas multipeak profiles occurred in others. Time to the early peaks was 1-2 h and those peaks were lower in amplitude than the peaks reached approximately 4.5 h after the application. Fig. 1 shows the mean plasma omeprazole concentration of the volunteers at different time intervals after a single dose of 20 mg of product "A" and "B" and Table I shows the mean values of C_{max}, $AUC_{0-\infty}$ and t_{max} for both

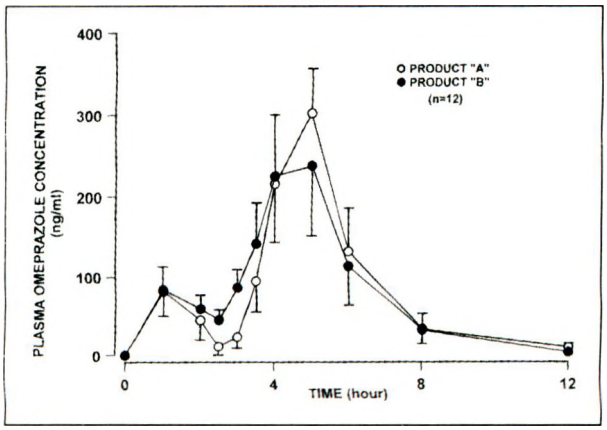

Fig. 1.: Plasma omeprazole concentrations (mean ± S.E.M.) at different time intervals after a single dose of 20 mg enteric-coated omeprazole capsules given 10-15 mins before breakfast in 12 healthy volunteers.

Table I. Comparative pharmacokinetics after a single oral dose of omeprazole (20 mg) in healthy volunteers. Values are expressed as mean±S.E.M.

Parameters	Product A	Product B
C_{max} (ng/ml)	361.2±71.1	317.7±85.8
t_{max} (h)	4.5±0.3	4.2±0.3
$AUC_{0-\infty}$ (ng/ml.h)	961±303	980±322

products. All of these parameters were not significantly different from each other.

When the results obtained from male and female subjects were reanalyzed separately, it was seen that the multipeak profile was more frequent and the amplitudes of the early peaks were significantly higher in female subjects ($p<0.05$; Figs. 2-4).

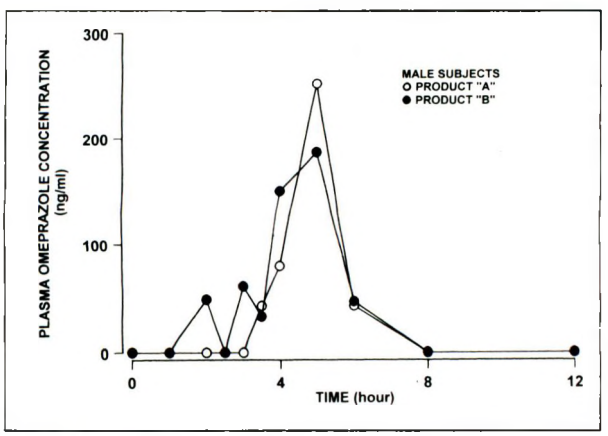

Fig. 2.: Median plasma omeprazole concentrations at different time intervals after a single dose of 20 mg enteric-coated omeprazole capsules given 10-15 mins before breakfast in 6 healthy male volunteers.

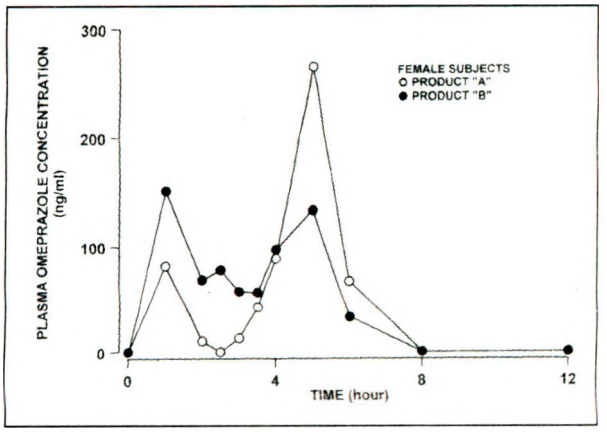

Fig. 3.: Median plasma omeprazole concentrations at different time intervals after a single dose of 20 mg enteric-coated omeprazole capsules given 10-15 mins before breakfast in 6 healthy female volunteers.

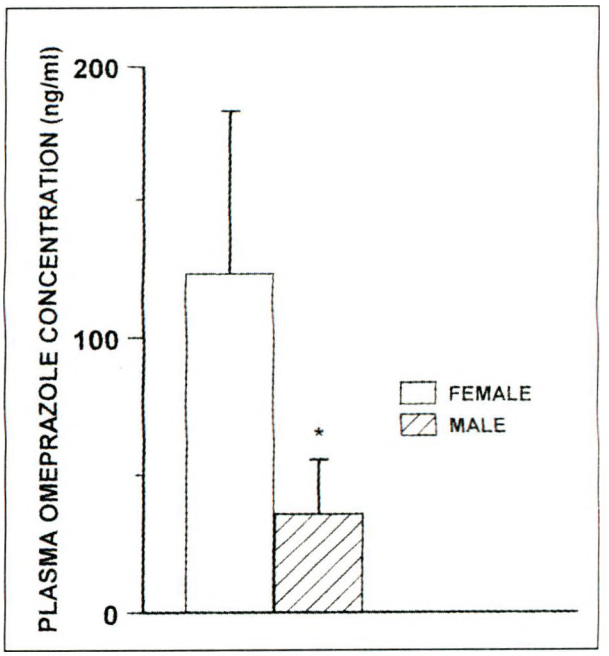

Fig. 4.: The amplitude of the early omeprazole peak plasma concentration reached 1-2 hrs. after a single dose of 20 mg enteric-coated omeprazole capsules given 10-15 mins before breakfast in female (n=6) and male (n=6) healthy volunteers. *$p<0.05$ vs female subjects.

DISCUSSION

In the present study, the area under the plasma omeprazole-time curve (AUC) was similar following both products. Although slightly (but not significantly) higher C_{max} values were obtained with product "A", product "A" and "B" may be considered to be bioequivalent since the degree

of suppression of gastric acid secretion was reported to be correlated to the AUC but not to the plasma concentration at any given time (4). The great intersubject variability in AUC values can be explained by 3 subjects being outlyers. Those subjects (1 female and 2 males) had the highest AUC values following both products. They may be slow metabolizers of omeprazole (6).

The omeprazole dosage recommended in the clinical programme was to be taken before breakfast. Andersson et al. (6) reported that the amount of omeprazole absorbed was unaffected by whether the capsules were taken before or after breakfast. The multipeak plasma concentration-time profile seen in this study was similar to those reported by Andersson et al. (6) when the drug was given before breakfast as in our case. Interestingly, although the investigators did not stress this, a single peak profile was obtained when omeprazole was taken after breakfast. Single peak profiles were also reported by several other investigators when they gave enteric-coated omeprazole preparations 2.5-3 hrs. after breakfast (7-9).

Enteric coating is accepted to prevent the granules releasing omeprazole until they reach the intestine and the rate of gastric emptying determines the time to absorption. The time to the first detectable plasma concentration was reported to be shorter after the drug given before breakfast (6). Therefore, the earlier of the omeprazole peaks in plasma may represent the omeprazole granules left in the stomach before food ingestion. It seems likely that the arrival of the remaining omeprazole granules to the intestinal lumen were delayed by food eaten 10-15 mins. after omeprazole.

The interesting observation of this study was the difference between the male and female subjects. It was seen that the multipeak profile was more frequent and the amplitudes of the early peaks were higher in female subjects. The design of this study and the number of subjects do not allow us to make any speculations on this finding. Further pharmacokinetic studies in both healthy volunteers and patients with peptic ulcer disease are needed to clearify the issue. Furthermore, the possibility of the gender difference on the suppression of gastric acid secretion by omeprazole must also be investigated.

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