Influence of food on the bioavailability of an enteric-coated tablet formulation of omeprazole 20 mg under repeated dose conditions

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ABR Thomson, P Sinclair, A Matisko, E Rosen, T Andersson, B Olofsson. Influence of food on the bioavailability of an enteric-coated tablet formulation of omeprazole 20 mg under repeated dose conditions. *Can J Gastroenterol* 1997;11(8):663-667. The objective of this study was to investigate the influence of food on the bioavailability of omeprazole (20 mg) given as an enteric-coated tablet under repeated dose conditions. This open randomized crossover study consisted of three seven-day treatment periods, each separated by a drug-free period. During each treatment period an enteric-coated tablet of omeprazole was taken once daily either under fasting conditions, or immediately before or after a standardized breakfast. On the last day of each treatment period, blood samples for the determination of plasma omeprazole concentrations were collected at baseline and at pre-determined intervals over the 24 h period following drug administration. Fifty-seven male and female subjects, aged 18 to 52 years, completed the study according to the protocol. No statistically significant differences were found when comparing either the before breakfast or after breakfast treatment regimens with the fasting regimen for the estimated mean area under the plasma concentration-time curve (AUC). The maximum plasma concentration was not found to differ significantly among any of the treatment regimens. However, the lower limit of the CI for the comparison of fasting/before breakfast was not contained within the limits of bioequivalence. The time to reach maximum plasma concentration was significantly different when fasting and after

breakfast regimens were compared. Thus, under repeated dose conditions, food has no influence on the bioavailability (expressed as AUC) of omeprazole given as the enteric-coated tablet formulation.

Key Words: Bioavailability, Enteric-coated tablet, Omeprazole

Influence de la prise d'aliments sur la biodisponibilité d'une formule de comprimé à enrobage entérique d'oméprazole 20 mg lors de doses répétées

RÉSUMÉ : L'objectif de cette étude était de mesurer l'influence de la prise d'aliments sur la biodisponibilité de l'oméprazole (20 mg) administré à répétition sous la forme de comprimés à enrobage entérique. Cette étude randomisée ouverte avec permutation des groupes portait sur trois périodes thérapeutiques de sept jours chacune, séparée d'un intervalle sans médicament. Lors de chaque traitement, un comprimé à enrobage entérique d'oméprazole a été administré une fois par jour, soit à jeun ou immédiatement avant ou après un petit déjeuner standardisé. Le dernier jour de chaque période thérapeutique, des prélèvements sanguins ont été recueillis pour mesurer les taux plasmatiques d'oméprazole au départ, puis à des intervalles

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prédéterminés au cours d'une période de 24 heures après l'administration du médicament. Cinquante-sept hommes et femmes, de 18 à 52 ans, ont mené l'étude à terme conformément au protocole. Aucune différence statistiquement significative n'a été observée lorsque l'on comparait les schémas thérapeutiques administrés avant ou après le petit déjeuner, avec le schéma administré à jeun pour ce qui est de l'estimation de l'aire moyenne sous la courbe concentration plasmatique-temps (ASC). La concentration plasmatique maximale n'a pas différé significativement entre les schémas thérapeutiques.

Toutefois, la limite inférieure de l'intervalle de confiance pour la comparaison entre le médicament administré à jeun/avant le petit déjeuner ne se trouvait pas dans les limites de la bioéquivalence. Le délai d'atteinte de la concentration plasmatique maximale a été significativement différent entre les schémas administrés à jeun et après le petit déjeuner. Ainsi, lors d'administrations répétées de la dose, la prise d'aliments n'a pas influé sur la biodisponibilité (exprimée sous forme d'ASC) de l'oméprazole administré en comprimé à enrobage entérique.

Omeprazole is a substituted benzimidazole that selectively inhibits the gastric enzyme H^+/K^+ -ATPase (proton pump) of the parietal cell. Omeprazole is effective in the inhibition of both basal and stimulated acid secretion, and is currently approved in Canada for the treatment of acid-related disorders, including duodenal and gastric ulcer, *Helicobacter pylori* eradication, reflux esophagitis, symptomatic reflux disease and Zollinger-Ellison syndrome. Omeprazole has been commercially available for the past seven years as encapsulated enteric-coated granules for oral administration.

A new enteric-coated tablet formulation of omeprazole has been developed. The clinically important end-point in acid-related diseases is the control of gastric acid secretion, which is correlated with the bioavailability of omeprazole, measured as the area under the omeprazole concentration-time curve (AUC) (1). We have demonstrated that this formulation is pharmacodynamically equipotent (percentage pH of at least 3) to the encapsulated enteric-coated granule formulation (2).

This tablet is emptied from the stomach as one unit due to the enteric coating, which dissolves only when pH is elevated to the extent found in the small bowel. Consequently, the bioavailability of the enteric-coated tablet depends, to a certain extent, on differences in rates of gastric emptying and on pyloric function. Therefore, it is important to assess any potential influence of food on the bioavailability of omeprazole given as an enteric-coated tablet.

SUBJECTS AND METHODS

This study was performed in accordance with the principles stated in the *Guidelines on Research Involving Human Subjects* issued by the Medical Research Council of Canada. The study protocol, which included the subject information and informed consent form, was approved by the Research Ethics Board for Human Experimentation, University of Alberta, Edmonton, Alberta.

Fifty-eight evaluable subjects were required to complete the study. Persons who discontinued prematurely were replaced in order to have 58 evaluable subjects for final analysis. Subjects were randomized to treatment according to a computer-generated randomization list.

After finalizing the protocol, it was decided that an interim analysis would be conducted when the first 36 evaluable subjects completed the study. The intention was to terminate the study if the predetermined stopping rule was

fulfilled. No additional subjects were enrolled until the interim analysis was completed. The study was to be stopped based only on results from the comparison between the mean AUCs under the fasting and the after breakfast conditions. A 96% CI was calculated for the mean AUC ratio. If this CI was within the accepted normal bioequivalence limits of 0.80 to 1.25, then bioequivalence was to be concluded between the fasting and after breakfast conditions. The study was to then be stopped and the full statistical analysis would be performed.

If this was not the case, additional subjects were to be included until 58 evaluable subjects had completed the study. The confidence level in the final analysis was set to 92%, and equivalence was to be concluded if the bioequivalence criterion was met. As a result, the overall confidence level for the study would be 90% and the overall power would be 0.80. The overall significance level for the two corresponding one-sided *t* tests would be 0.05.

Male and female healthy subjects between 18 and 55 years old, with a body mass index between 19 and 27 kg/m², were enrolled. Subjects were randomized if their baseline clinical and laboratory findings were normal. Signed informed consent was obtained from each person. Volunteers with significant clinical illness within two weeks of randomization and those who required concomitant medication during the study were not randomized. Subjects with severe allergic disease or a history of cardiac, renal, hepatic or gastrointestinal disease were not randomized. Subjects known or suspected to abuse drugs and/or alcohol were also excluded. The *H. pylori* status of the volunteers was not assessed.

The study was conducted as an open randomized cross-over trial consisting of three seven-day treatment periods, each separated by a drug-free interval of at least seven days. At a pre-entry screening visit, subjects underwent a full clinical examination to determine eligibility before randomization. Laboratory investigations were repeated within five days after the last clinic visit. During each treatment period, an enteric-coated tablet containing 20 mg omeprazole was taken once daily, according to one of the following three treatment regimens: under fasting conditions (maintained for 4 h after drug intake); immediately before breakfast; or immediately after breakfast. On the last day of each treatment period (the investigational day), blood samples were collected at baseline and at predetermined intervals over the 24 h period following drug administration to determine the plasma omeprazole concentrations.

Figure 1) Mean plasma time-concentration curves (nmol/L) following administration of 20 mg omeprazole as an enteric-coated tablet in the following three treatment protocols: fasting (□); before breakfast (●); and after breakfast (Δ)

During the first six days of each treatment period, subjects took the enteric-coated omeprazole tablet at home. On these days subjects chose a breakfast option that was considered to be nutritionally equivalent to the standardized breakfast that they would receive on the investigational day. Alcohol consumption was prohibited during the two days preceding each treatment period and throughout each treatment period. All medications (including over-the-counter drugs) were prohibited during the two days preceding each treatment period and throughout each treatment period (with the exception of birth control drugs).

On each investigational day, subjects arrived at the clinical investigation unit at approximately 07:30, having fasted since 22:00 the previous day. A reference blood sample was collected, after which the study drug was administered with 200 mL water. Subsequent blood samples were taken every half hour up to 12 h, and thereafter every hour up to 24 h. The plasma phase was kept frozen at -20°C until analysis for omeprazole using a validated high pressure liquid chromatography method (3). Standardized meals were served at 08:00, 12:00 and 18:00, and an evening snack was given at 21:00.

Routine clinical laboratory examinations were performed at the Department of Clinical Chemistry, University of Alberta Hospital, Edmonton, Alberta using routine methods. If clinically abnormal values were observed, the relevant laboratory screens were repeated; subjects exhibiting continued clinically significant abnormal values were not included in the study, or, if already included, were withdrawn from further participation and were followed for as long as was clinically necessary.

Adverse event data collected included information spontaneously reported by the subjects and in response to active questioning, as well as information revealed by physical examination or other diagnostic procedures. The safety analysis included all subjects who took at least one dose of the

Figure 2) Plasma concentrations (nmol/L) in a representative subject following administration of 20 mg omeprazole as an enteric-coated tablet in the following three treatment protocols: fasting (□); before breakfast (●); and after breakfast (Δ) in one representative subject

study drug and for whom subsequent safety data were available.

The only statistical approach to the analysis of efficacy data was the per protocol analysis that included all persons who successfully completed the protocol with no major violations. Bioavailability of omeprazole was expressed as the AUC from time zero to the time of the last determinable plasma omeprazole concentration. The trapezoidal method was used to calculate the AUC, and the results were expressed in $\mu\text{mol} \times \text{h/L}$. The observed maximum plasma concentration (C_{max}) and the time to reach the first observed maximum plasma concentration (t_{max}), were also recorded. Both AUC and C_{max} were analyzed in a model corresponding to the three-way crossover design with factors for subject, period and treatment.

CI's (with an overall confidence level of 90%) for the mean ratio of before breakfast:fasting regimens and after breakfast:fasting regimens were reported for these variables. Student's t distribution was used on the log-transformed values in these calculations. Corresponding P values were also reported. There were 10 instances in which the baseline plasma omeprazole level was not at zero (range 12 to 228 μmol). In the calculation of AUC for the final analysis, the baseline plasma omeprazole value at time zero was set to zero for these subjects to avoid overestimation of the AUC. The statistical software used was the SAS system on VMS V6.07 (SAS statistical software, SAS Institute, North Carolina).

RESULTS

Sixty subjects were enrolled in the study and all were randomized to treatment; three of the 60 were not included in the per protocol analysis and one was not included in the safety evaluation. One subject was mistakenly randomized into the study. Another subject withdrew from the study due to headaches during the first treatment period so a replace-

TABLE 1
Study variables following administration of 20 mg omeprazole as the enteric-coated tablet before and after breakfast, and under fasting conditions in 57 healthy subjects

Variable	After breakfast	Before breakfast	Fasting
AUC ($\mu\text{mol} \times \text{h/L}$)			
Estimated mean	2.235	2.268	2.399
95% CI	1.790-2.792	1.816-2.833	1.921-2.99
C_{max} ($\mu\text{mol/L}$)			
Estimated mean	1.339	1.421	1.301
95% CI	1.145-1.566	1.215-1.662	1.112-1.521
t_{max} (h)			
Mean	3.50	2.50	2.21
SD	1.60	1.75	1.05
Median	3.50	2.00	2.00
Range	0.50-7.00	0.50-6.50	1.00-4.50

AUC Mean area under the plasma concentration-time curve; C_{max} Maximum plasma concentration; t_{max} Time to reach the first observed maximum plasma concentration

TABLE 2
Ratios for AUC and C_{max} following administration of 20 mg omeprazole as the enteric-coated tablet for fasting/before breakfast conditions and fasting/after breakfast conditions in 57 healthy subjects

Mean ratio	Estimate	92% CI		P
		Lower	Upper	
AUC ($\mu\text{mol} \times \text{h/L}$)				
Fasting/before	1.057	0.949	1.178	0.3631
Fasting/after	1.073	0.963	1.195	0.2505
C_{max} ($\mu\text{mol/L}$)				
Fasting/before	0.915	0.789	1.061	0.2925
Fasting/after	0.972	0.838	1.126	0.7307

AUC Mean area under the plasma concentration-time curve; C_{max} Maximum plasma concentration

ment was found. A third subject took the study medication before coming to the clinical investigation unit on day 7, and consequently the first four blood samples (postdrug intake) were missing. Analysis of the remaining samples for this subject revealed that the peak plasma concentration had been missed. This was considered a major protocol deviation, so this subject was withdrawn after the second treatment period and was excluded from analysis. Replacement of this subject was logistically difficult. It was calculated that inclusion of a replacement person would increase the overall power of the study by less than 1%; therefore, it was decided not to replace this subject.

The remaining 57 subjects (24 males and 33 females) completed the study according to protocol. They had a mean age of 27 years (range 18 to 52), mean weight of 70 kg (range 50 to 93) and a mean height of 170 cm (range 160 to 190). Two subjects were Asian, one was of African descent and

one was Trinidadian; the remaining 53 subjects were Caucasian.

Eighteen subjects continued use of prescribed medications during the study, and 19 subjects occasionally used over-the-counter drugs during the study. None of these medications was considered to affect the primary variable in this study, measurement of plasma omeprazole concentrations.

For the interim analysis, the 96% CI for the mean ratio between the AUCs under the fasting and the after breakfast conditions was 0.899 to 1.256, $P=0.4502$.

The mean plasma concentration-time curves of the 57 subjects are presented in Figure 1, and the plasma concentrations in a representative subject are shown in Figure 2. In 28 of the 57, the AUC of omeprazole was decreased following administration immediately after breakfast compared with administration under fasting conditions. The estimated mean AUC was $2.235 \mu\text{mol} \times \text{h/L}$ when the tablet was given after breakfast, compared with $2.399 \mu\text{mol} \times \text{h/L}$ when given under fasting conditions (Table 1). This difference was not statistically significant ($P=0.2505$). When the tablet was administered immediately before breakfast, 32 of 57 individuals exhibited a decreased AUC, compared with that of subjects under fasting conditions. The estimated AUC was $2.268 \mu\text{mol} \times \text{h/L}$ when the enteric-coated tablet was given before breakfast, and this value was not significantly different from that under fasting conditions ($P=0.3631$). Both of the 92% CIs for the mean ratios of AUC were within the limits (0.80 to 1.25) for bioequivalence (Table 2). Because an interim analysis was done, sample size had to be adjusted as well as the level of significance. In order to maintain a 90% CI in the final ratio analysis, the level of significance was set at 0.02 which translates to the 92% CI. This consumes the overall significance in the final analysis.

Regarding C_{max} , there were no statistically significant differences between either of the fed regimens compared with the fasting condition (Table 1). The 92% CI for the mean ratio of C_{max} for fasting/after breakfast was within the standardized limits (0.80 to 1.25) for bioequivalence. However, the 92% CI for the fasting/before breakfast comparison was not entirely contained within these limits (the lower limit of the fasting/before breakfast interval was 0.789) (Table 2).

A statistically significant prolongation in mean t_{max} of approximately 1.3 h was seen when the tablet was administered after breakfast versus when fasting ($P=0.0001$, Table 1). However, there was no statistically significant difference in t_{max} between the before breakfast and fasting conditions ($P=0.6109$).

Fifty-nine of the 60 enrolled subjects were eligible for evaluation of adverse events. Seventy-eight adverse events were recorded for 34 persons during the omeprazole treatment periods and 34 adverse events were reported for 22 subjects during the washout periods. The pattern of specific adverse events was not different from that previously documented during omeprazole treatment.

DISCUSSION

The degree of acid suppression achieved during omeprazole treatment is directly correlated with AUC (1). Therefore, it is important when evaluating a new formulation of omeprazole, such as the enteric-coated tablet, that bioequivalence to the existing formulation (encapsulated enteric-coated granules) can be established.

The results of the present study show that there is no significant food interaction under repeated dose conditions, whether the omeprazole enteric-coated tablet is given before or after breakfast, compared with fasting conditions. The mean AUCs under repeated dose conditions for all treatment regimens are higher than those previously reported during single dose studies. These findings are in agreement with results previously obtained with the encapsulated enteric-coated granules: during repeated dosing, the AUC increased over the single-dose AUC by 69% for a 20 mg dose of omeprazole (4). S-mephenytoin hydroxylase, part of the cytochrome P₄₅₀ system, is the major omeprazole metabolizing enzyme (5). The major reason for the increase in AUC during repeated dosing is probably a result of decreased first-pass metabolism of omeprazole, which is likely a function of partial inhibition of the isoenzyme S-mephenytoin hydroxylase caused by omeprazole.

While there were no statistically significant differences between the C_{max} values for either the after or before breakfast regimens compared with fasting conditions, the 92% CI for the mean ratio of C_{max} for the fasting/before breakfast comparison did not fall entirely within the limits for bioequivalence. However, this does not affect the conclusion of the study, because bioequivalence is based on the AUC and not on C_{max}. Furthermore, control of gastric acid secretion has been shown to be correlated to AUC but not to C_{max}.

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(1). The value of t_{max} was prolonged when the tablet was administered after breakfast compared with under fasting conditions (Table 1). The reason for this difference was not established in this study, but may relate to the fact that the tablet was in the stomach longer, potentially giving a longer t_{max}.

It has been hypothesized that the lower AUC observed with single dosing may also be a result of degradation of omeprazole by gastric acid, degradation that would not occur when acid is suppressed (as would be the case during repeated dosing). Interestingly, no statistically significant difference in AUC of the encapsulated enteric-coated granules has been observed in subjects studied under both untreated and acid-suppressed conditions (6). However, because the number of subjects in that study was low (n=8), the 20% increase in mean AUC reported under acid-suppressed conditions might have reached statistical significance if more subjects had been included. Furthermore, the enteric-coated tablet formulation of omeprazole may remain in the stomach for a longer period, resulting in prolonged exposure to acid (longer t_{max}), and possible acidic degradation under single dose conditions. During repeated dose conditions, the gastric acidity is reduced due to the effect of omeprazole, so potential acidic degradation of omeprazole is less likely. Interestingly, the t_{max} does not seem to be affected as much by food during repeated dosing as it is during single dosing.

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