Pharmacokinetics and pharmacodynamics during treatment with the omeprazole 20 mg enteric-coated tablet and 20 mg capsule in asymptomatic duodenal ulcer patients

ABR Thomson MD PhD FRCPC FACG, P Kirdeikis RN, R Lastiwka RN, K Röhss PhD, P Sinclair MSc, B Olofsson PhD

ABR Thomson, P Kirdeikis, R Lastiwka, K Röhss, P Sinclair, B Olofsson. Pharmacokinetics and pharmacodynamics during treatment with the omeprazole 20 mg enteric-coated tablet and 20 mg capsule in asymptomatic duodenal ulcer patients. *Can J Gastroenterol* 1997;11(8):657-660. This study compared the 24 h intragastric pH profile and bioavailability at repeated dosing conditions of the omeprazole 20 mg enteric-coated tablet versus the 20 mg capsule. Forty duodenal ulcer patients in asymptomatic remission completed this randomized open two-way crossover study. Omeprazole 20 mg tablets or capsules were administered for seven days in each period. A 24 h pH recording was performed before the start of treatment and on day 7 of each treatment period. Plasma concentrations of omeprazole were determined 24 h after the dose. The treatment periods were separated by two to four weeks. The difference in percentage of time with pH of at least 3 was less than 16% in favour of the tablet (not significant). The estimated mean area under the plasma concentration-time curve as well as the maximum plasma concentration (C_{max}) for omeprazole were 18% and 41% higher, respectively, for the tablet versus the capsule, with the latter percentage being statistically significant. The time to reach C_{max} (t_{max}) with the tablet was, on average, about 0.5 h longer than to reach the t_{max} of the capsule. This study indicates that the enteric-coated tablet formulation of omeprazole is biodynamically equivalent to the capsule regarding their effects on intragastric pH during repeated dosing.

Key Words: Bioavailability, Intragastric pH profile, Omeprazole capsule, Omeprazole enteric-coated tablet, Repeated dosing conditions

Pharmacocinétique et pharmacodynamie du traitement par oméprazole 20 mg en comprimé à enrobage entérique et en capsule dans les cas d'ulcère duodénal asymptomatique

RÉSUMÉ : Cette étude visait à comparer le profil du pH intragastrique sur 24 heures et la biodisponibilité de plusieurs doses d'oméprazole 20 mg en comprimé à enrobage entérique et en capsule. Quarante patients atteints d'ulcères duodénaux en rémission asymptomatique ont complété cette étude ouverte et randomisée avec permutation des groupes dans les deux sens. Les comprimés ou les capsules d'oméprazole 20 mg ont été administrés pendant sept jours lors de chacune des périodes. Un enregistrement du pH sur 24 heures a été effectué avant le début du traitement, puis au jour 7 de chacune des périodes thérapeutiques. Les concentrations plasmatiques d'oméprazole ont été mesurées 24 heures après l'administration de la dose. Les périodes thérapeutiques ont été séparées d'intervalles de deux à quatre semaines. La différence quant au pourcentage de temps durant lequel le pH a été au moins à 3 a été inférieure à 16 % en faveur du comprimé (non significatif). La moyenne sous la courbe de concentration plasmatique-temps estimée (ASC), de même que la concentration plasmatique maximum (C_{max}) de l'oméprazole ont été de 18 et de 41 % supérieures, pour le comprimé et la capsule respectivement, le dernier pourcentage étant statistiquement significatif. Le délai d'atteinte de la C_{max} (t_{max}) du comprimé a été en moyenne plus long d'environ 0,5 h que celui de la capsule. Cette étude révèle que l'oméprazole en comprimé à enrobage entérique est équivalente l'oméprazole en capsule sur le plan biodynamique pour ce qui est des effets sur le pH intragastrique lors d'une administration répétée.

Division of Gastroenterology, University of Alberta, Edmonton, Alberta; Astra Pharma Inc, Mississauga, Ontario; Astra Hässle, Gothenburg, Sweden
Correspondence and reprints: Dr ABR Thomson, University of Alberta, 519 Robert Newton Research Building, Edmonton, Alberta T6G 2C2.

Telephone 403-492-6490, fax 403-492-7964, e-mail alan.thomson@ualberta.ca

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The 20 mg omeprazole capsule contains enteric-coated granules of omeprazole. The manufacturing granulation process is complicated, and therefore a tablet that is easier to produce has been developed. Tablets, compared with capsules, can easily be dispensed in convenient packages, such as blister cards.

The omeprazole tablet is not pharmacokinetically bioequivalent with the enteric-coated granule capsule formulation (1). The formulations are, however, equipotent in terms of their inhibitory effect on peak acid output. The rate of duodenal ulcer healing is directly correlated to the reduction in 24 h intragastric acidity (2). Accordingly, this study was performed to compare the omeprazole 20 mg tablet with the 20 mg capsule at repeated doses in terms of the 24 h intragastric pH profile, as well as the bioavailability – area under the omeprazole concentration-time curve (AUC), observed maximum plasma concentration ($C_{\max}$) and the time to reach $C_{\max}$ ($t_{\max}$).

PATIENTS AND METHODS

Forty duodenal ulcer patients who were in asymptomatic remission at pre-entry evaluation were to be recruited for the study. Inclusion criteria were history of duodenal ulcer disease confirmed on endoscopy with characteristic symptoms in the past 36 months; no moderate or severe ulcer-like dyspeptic symptoms during the month preceding study entry; 18 to 65 years old; baseline gastric acidity (intragastric pH below 3 for at least 25% of the time in the baseline 24 h pH recording); and signed informed consent.

Exclusion criteria were treatment with any acid antisecretory or prokinetic drugs in the week preceding the study, or a known requirement for any of these drugs during the study interval; history of pyloric stenosis or gastric surgery, with the exception of simple closure of a perforation; significant disease that might interfere with the study or place the patient at risk during the study; alcoholism, drug abuse or any other circumstances that might interfere with the patient's ability to comply with the study requirements; and women who were pregnant, breast-feeding or of child-bearing potential not practising adequate contraception.

Antacids were allowed in the study drug-free periods. Subjects were encouraged not to take any antacids while on omeprazole. Subjects who were smokers abstained from smoking during the 24 h admissions to the clinical investigation unit.

Study design: This randomized open crossover trial consisted of two seven-day periods during which 20 mg omeprazole was given once daily, either as an enteric-coated tablet or a capsule. Each patient underwent three 24 h pH recordings, one within two weeks of the first period (baseline), and then one during the last day of each of the two periods. Blood samples to determine omeprazole plasma concentrations were also collected over the 24 h following the last dose in each treatment period. The treatment periods were separated by two to four weeks.

The 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,

which encompasses the Declaration of Helsinki. Subjects were free to discontinue participation in the study at any time without prejudice to further treatment. Also, the subject's participation in the study could be discontinued at any time at the discretion of the investigator.

Therapy: The omeprazole 20 mg enteric-coated tablets contained omeprazole magnesium as the active ingredient. The formulation was a tablet with a core of omeprazole magnesium salt and constituents covered with a high acid-resistant, rapid-release coating. The 20 mg capsule contained enteric-coated granules of omeprazole and constituents filled in a hard gelatin capsule.

Patients took one tablet or one capsule with a glass of water each morning at 08:00, just before consuming breakfast.

Patients were asked to refrain from excessive alcohol consumption (more than three drinks/day) during the study and to abstain from alcohol for 24 h before each pH recording.

Study procedures: Patients remained in the clinical investigation unit for the duration of the 24 h pH recording. They arrived at 07:00 on each study day, having fasted since 22:00 the previous day. On study days during treatment, an indwelling cannula was inserted into a forearm vein at approximately 07:20. The cannula was used for blood sampling to determine omeprazole concentration in plasma.

At approximately 07:40, a calibrated pH microelectrode (Ingold bipolar glass; Solothurn), attached to a data logger (Mark II Gastrograph, Medical Instruments Corporation AG, Solothurn, Switzerland), was passed transnasally and placed at a standard distance of 50 cm from the nares to position the electrode in the midfundus of the stomach. The electrode was connected to a battery-powered data logger with a 96 kbyte memory (Mark II Gastrograph). A two-point calibration of the electrode was performed at room temperature at the start and termination of each 24 h recording using standard buffers of pH 7.38 and pH 1.10.

The Mark II Gastrograph measured the potential difference between the recording and reference electrodes in the tip of the probe four times per second, and calculated and stored a median value every 6 s. These microvolt data were converted into pH by an analysis program (Software PAC2, Medical Instruments Corporation AG). The Gastrograph data were transferred to a personal computer for subsequent analysis.

At approximately 08:00 the patient took the study drug with a glass of water, and the pH recording was started. Standardized meals were served at 08:30, 12:00, 18:00 and 20:00. Each patient consumed the same quantity of food and drink during all pH recordings.

Venous blood samples were drawn from an indwelling forearm cannula 5 mins before the omeprazole dose and every 30 mins after the dose for 12 h, with further measurements at 13, 14, 18 and 24 h after the dose. Omeprazole concentrations were analyzed at Bioanalytical Chemistry, Astra Hässle AB, Gothenburg, Sweden using liquid chromatography (3). The intraday (repeatability) coefficient of variation was 1.3%, and the interday (reproducibility) coefficient of variation was 2.3%.

Figure 1) Median 24 h pH profiles during baseline and following administration of 20 mg omeprazole as an enteric-coated (EC) tablet and as a capsule in 39 duodenal ulcer patients in asymptomatic remission. The mean ratio for percentage of time with pH 3 or greater following omeprazole as either an EC tablet or a capsule was estimated to be 1.07 (90% confidence interval 0.99 to 1.16, $P=0.130$)

Physical examination, including routine electrocardiogram and laboratory tests, was performed within two weeks of the last pH recording. Routine hematology, blood chemistry and urinalysis were done before and after the study as part of the physical examination, with samples analyzed by the University of Alberta Hospital laboratory.

Statistical methods and plans for analysis: The percentage of time with pH of at least 3 and the median 24 h pH were calculated for each patient and each recording period using the Software Pac2 program (M/C, Solothurn, Switzerland).

Bioavailability was calculated as the AUC from time zero to the last determinable omeprazole plasnatration using the trapezoidal method. AUC was expressed as $\mu\text{mol} \times \text{h/L}$. C_{max} ($\mu\text{mol/L}$) and t_{max} (h) were also calculated for each subject.

The study was analyzed according to a two-period, two-sequence crossover analysis. A general linear model, including sequence, period and treatment as fixed effects and 'subject within sequence' as a random effect, was used to analyze the logarithms of the proportion of time with pH 3 or greater, as well as the logarithms of AUC and C_{max} . Wilcoxon's rank-sum test was used to analyze t_{max} .

A supplementary exploratory analysis was performed apart from the main analysis. Patient 17 was excluded; the percentage time with pH at least 3 obtained for this subject showed a considerable deviation from the expected linear relationship formulated from results obtained from the other patients. This subject was therefore excluded from further analysis. To estimate the impact of this extreme value, a supplementary statistical evaluation was performed with this subject excluded.

To assess bioequivalence, 90% CIs were calculated for the mean ratios of percentage time with pH 3 or greater, AUC and C_{max} , comparing tablet with capsule. Estimates of the means of the treatment effects were calculated, and 95% CIs were constructed. The CIs were calculated by using the mean square error from the appropriate ANOVA and quintiles from Student's distribution. To obtain the correct estimates and CIs for percentage of time with pH 3 or greater, AUC and C_{max} , calculations were first performed

TABLE 1

Mean area under the plasma concentration-time curve (AUC), observed maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) following administration of 20 mg omeprazole

	Omeprazole formulation	
	Capsule	Tablet
AUC ($\mu\text{mol} \times \text{h/L}$)		
Estimated mean	1.85	2.15
95% CI	1.39-2.45	1.62-2.86
C_{max} ($\mu\text{mol/L}$)		
Estimated mean	1.09	1.53
95% CI	0.92-1.31	1.28-1.83
t_{max} (h)		
Mean	1.59	2.03
SD	1.39	1.65
Median	1.08	1.08
Range	0.50-6.08	1.08-8.08

TABLE 2

Mean ratios for mean area under the plasma concentration-time curve (AUC) and observed maximum plasma concentration (C_{max}) following administration of 20 mg omeprazole as an enteric-coated tablet and a capsule

Mean ratio tablet:capsule	90% confidence interval			
	Estimated	Lower	Upper	P
AUC	1.17	1.05	1.29	0.015
C_{max}	1.40	1.23	1.59	0.000

on the log-transformed values before calculating the anti-logarithms.

Descriptive statistics were determined for all variables. Initially it was considered that an equivalence with statistical significance could be detected by using a sample size of 12 subjects. After further statistical analysis of data from a previous study, 40 patients were deemed to be required to determine such an equivalence, and therefore the protocol was amended to include a larger number of volunteers. The statistical software used was the SAS system on MVS V6.07 (SAS Institute, North Carolina).

RESULTS

Patient description: Forty-three volunteers were recruited. Two were discontinued from the study, one did not fulfil the inclusion criteria of baseline gastric acidity (a baseline gastric pH of at least 3 for more than 25% of the time) and one discontinued at the baseline assessment due to a personal reason. One patient was replaced due to protocol deviation. The randomization order was maintained for the replaced patient. Forty persons completing the study as per protocol, 28 males and 12 females, mean age 43 years (range 22 to 60), mean weight 79.9 kg (range 45 to 146) and mean height 171 cm (range 146 to 187). All subjects were Caucasian except for one of African and one of East Indian descent. Nineteen participants were smokers.

Figure 2) Percentage time with pH 3 or greater following administration of 20 mg omeprazole as an enteric-coated tablet compared with a capsule in 40 duodenal ulcer patients in asymptomatic remission. The line of identity is indicated. Patient 17 was excluded from analysis

Figure 3) Mean omeprazole plasma concentrations following administration of 20 mg omeprazole as an enteric-coated tablet (■) and a capsule (○) in duodenal ulcer patients in asymptomatic remission. Patient 17 was excluded from further analyses

Pharmacodynamics: There were no major differences between the two omeprazole formulations regarding the median pH profile (Figure 1). The estimated mean for the percentage of time with pH 3 or greater was 57.4% for the omeprazole tablet versus 50.7% for the capsule (not statistically significant). In addition, the confidence interval for percentage of time with pH 3 or greater (1.16) was within the 90% CI accepted for bioequivalence studies (0.80 to 1.25). There was a linear relationship between the percentage time with pH 3 or greater following administration of 20 mg omeprazole as an enteric-coated tablet and a capsule (Figure 2).

Pharmacokinetics: The estimated mean values for AUC and C_{max} , and the mean ratios of AUC and C_{max} comparing tablet with capsule, along with the descriptive listings for t_{max} , are presented in Tables 1 and 2. Mean plasma profiles were similar whether omeprazole was given as tablet or a capsule. C_{max} was higher after administration of the tablet (Figure 3).

The AUC was higher in 24 of 40 patients when omeprazole was given as a tablet versus as a capsule; this resulted in a 17% higher estimated mean AUC of $2.15 \mu\text{mol} \times \text{h/L}$ for the tablet compared with $1.85 \mu\text{mol} \times \text{h/L}$ for the capsule. This difference was statistically significant. Thirty of the 40 subjects (75%) had a higher C_{max} after the tablet (40% higher) than after the capsule, a difference that was statistically significant (Table 2). The 90% CIs for the AUC and C_{max} mean ratios of tablet:capsule were not within the 90% CI accepted for bioequivalence.

The t_{max} values of omeprazole showed individual variation. In approximately half of the patients the tablet exhibited a prolonged t_{max} compared with the capsule (on average about 0.5 h); this difference was statistically significant ($P=0.036$).

DISCUSSION

The clinical effect of acid secretion inhibitors is correlated with the reduction in 24 h intragastric acidity (2). Thus, the primary aim of this study was to compare the two omeprazole formulations in terms of percentage of time with pH 3 or greater. There was no statistically significant difference between the tablet and the capsule – the difference in the time with pH 3 or greater between the formulations was decreased to 16% or less, which corresponds to a maximum of 2 h. The accepted CI for bioequivalence is 0.8 to 1.25. Therefore, we found it reasonable to regard the two formulations as equipotent.

Compared with the capsule, the tablet is emptied from the stomach as one unit due to the enteric coating which dissolves only when the pH is elevated to the extent found in the small bowel. Consequently, the absorption and first-pass metabolism of the omeprazole from the tablet take place in a shorter time. We speculate that this may be the reason for the observed differences in AUC, C_{max} and t_{max} . However, these small differences in bioequivalence were insufficient to result in differences in acid inhibitory effects.

CONCLUSIONS

The tablet and capsule formulations of omeprazole were not bioequivalent regarding plasma omeprazole AUC, C_{max} or t_{max} . However, the tablet formulation of omeprazole is equipotent to the capsule regarding their effects on intragastric pH during repeated dose concentrations.

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