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Effect of timing of dosing in relation to food intake on the pharmacokinetics of esomeprazole

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What is already known about this subject
Systemic esomeprazole exposure is decreased when administered simultaneously with food.

What this study adds
Taking esomeprazole within 15 min of eating a high-fat, high-calorie meal results in reduced systemic drug exposure.

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Aim
To investigate the pharmacokinetics of esomeprazole before a high-fat meal *vs.* fasting.

Methods
This open-label, randomized, crossover study consisted of two 5-day dosing periods of esomeprazole 40 mg per day. On days 1 and 5, subjects received esomeprazole 15 min before a high-fat meal (fed) or 4 h before a non-high-fat meal (fasting).

Results
On days 1 and 5, ratio of fed to fasting area under the plasma concentration–time curve [0.56, 90% confidence interval (CI) 0.50, 0.64, and 0.78, 90% CI 0.74, 0.82, respectively] and peak plasma concentration (0.34, 90% CI 0.28, 0.41, and 0.47, 90% CI 0.41, 0.52, respectively) were outside of the limits of bioequivalence.

Conclusions
Esomeprazole bioavailability was reduced when taken within 15 min before eating a high-fat meal *vs.* that while fasting.

Introduction

Esomeprazole, the *S*-isomer of the racemate omeprazole, is a proton pump inhibitor (PPI) used to treat acid-related disorders, including gastro-oesophageal reflux disease and erosive oesophagitis and their symptoms [1, 2]. The pharmacodynamic effect of esomeprazole, inhibition of gastric acid secretion and percentage of time with intragastric pH > 4.0, correlates with its area under the plasma concentration–time curve (AUC) [3, 4]. However, esomeprazole AUC is decreased when administered simultaneously with food [4]. The effect of timing of food and administration of esomeprazole on the pharmacokinetic profile of esomeprazole has not been studied previously. Therefore, the objective of this study was to compare the effects of dose administration, 15 min before eating *vs.* under fasting conditions, on the pharmacokinetics of esomeprazole on the first day of dosing and at steady state (day 5) in healthy volunteers.

Methods

Subjects

Healthy adults (aged 18–50 years, inclusive) with a body weight within 20% of ideal for their height and frame were eligible to participate. Inclusion and exclusion criteria were consistent with those of a previous pharmacokinetic study [5], except that subjects in the present study did not need to accept a nasogastric tube, nor were they screened for *Helicobacter pylori* infection or cytochrome P450 2C19 polymorphism. Subjects were required to sign informed consent statements before enrolment and to comply with study procedures. The study protocol was approved by the Institutional Review Board at MDS Pharma Services (Lincoln, NE, USA) and study procedures were performed in accordance with the ethical principles of the Declaration of Helsinki [6] and its amendments and in compliance with Good Clinical Practice regulations [7].

Study design

In this single-centre (MDS Pharma Services), open-label, randomized, two-way crossover trial (NEXIUM Study 314), subjects were randomly assigned to one of two dosing sequences, each consisting of two 5-day dosing periods separated by a 7–14-day wash-out period. In one dosing period, on days 1 and 5, subjects received esomeprazole 40-mg capsules 15 min before a standardized, high-fat meal (fed) consisting of eggs, bacon, buttered toast, hash brown potatoes and whole milk. In the other dosing period, on days 1 and 5, subjects received esomeprazole 40 mg 4 h before a standardized, non-high-fat meal (fasting). On days 2–4 of both dosing periods, esomeprazole was administered 30 min before a standardized, medium-fat breakfast. Subjects remained at the study centre for the entire 5 days of each study period.

Pharmacokinetic and statistical analyses

On days 1 and 5 of each dosing period, 5-ml venous blood samples were collected from each subject 5 min before and 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, 10.0 and 12.0 h after dose administration. The samples were collected in heparinized tubes and centrifuged. Plasma was shipped frozen to Quintiles AB (Uppsala, Sweden) for analysis using an achiral column, normal-phase liquid chromatography, and UV detection [8]. The lower limit of quantification (LOQ) was 25 nmol l^{-1}. Interassay repeatability and inaccuracy were calculated from control sample concentrations of 50, 500 and 6000 nmol l^{-1}. Control samples were analysed twice in each analytical run. The interassay repeatability was 4.9%, 3.2% and 2.8% for each concentration, respectively, and the inaccuracy was 0.9%, −1.3% and −1.3%, respectively.

The primary variables were maximum plasma concentration (C_{max}) and AUC. AUC was calculated as $AUC_{0-t} + C_t/\lambda_z$, where AUC_{0-t} was AUC from time 0 to the time of the last quantifiable esomeprazole concentration (linear trapezoidal method), C_t was the last quantifiable esomeprazole concentration and λ_z was the terminal phase elimination rate constant. Secondary variables were AUC_{0-t}, time to maximum plasma concentration (t_{max}) and elimination half-life ($t_{1/2}$, defined as $0.693/\lambda_z$). To ensure sufficient data were available to calculate AUC, the percentage extrapolated of AUC_{0-t} could not exceed 20%. On day 1, AUC data were analysed as a single-dose treatment and extrapolated to infinity. On day 5, AUC was extrapolated from time 0–24 h as $AUC_{0-24} = AUC_{0-t} + [1 - \exp(-\lambda_z) \bullet (24 - t)] \bullet C_t/\lambda_z$, where C_t and t were the last quantifiable concentrations and the corresponding time and λ_z was the terminal phase elimination rate constant and represented one dosing interval under multiple-dosing steady-state conditions. The observed C_{max} and t_{max} were recorded. Concentration data below the LOQ occurring before C_{max} were assigned a value of 0, and those occurring after C_{max} were excluded from pharmacokinetic analysis.

Subjects were considered evaluable if they finished both treatment periods without major protocol violations and had sufficient data to determine both primary variables (AUC and C_{max}). Plasma concentrations were summarized by the following procedure: if ≥50% of concentrations were not quantifiable, mean and standard deviation (SD) were not calculated; if <50% of concentrations were not quantifiable, a value of 12.5 nmol l^{-1} was assigned for each concentration below LOQ to calculate mean and SD. AUC and C_{max} were logarithm-transformed and analysed using an analysis of variance (ANOVA) model fitted for the effects of sequence and subjects within sequence, period and feeding regimen. Contrasts between regimens were calculated and the results presented as geometric least-square mean of the ratio of fed *vs.* fasting with its 90% confidence interval (CI). Bioequivalence was concluded if the 90% CIs fell within the range of 0.80–1.25. Results for t_{max} were summarized using median and range; $t_{1/2}$ was summarized using mean and SD.

Previous pharmacokinetic studies suggested that the variability in AUC and C_{max} (fed *vs.* fasting) would be 10% and 15%, respectively, below the bioequivalence limit of 20%. A sample-size population of 36 evaluable subjects was estimated to provide 95% overall power (97.5% for either C_{max} or AUC) to show 'no food effect' with a significance level of 0.05.

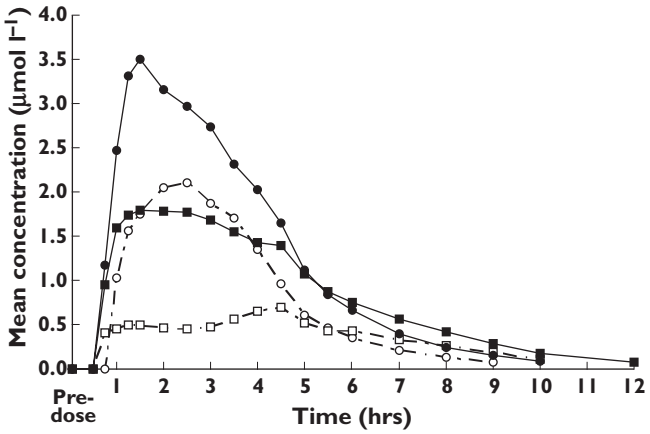

Figure 1

Mean plasma esomeprazole concentration *vs.* time on days 1 and 5 for subjects ($N = 44$) eating 15 min (fed) or 4 h (fasting) after esomeprazole administration. (–○ -, Day 1 Fasting; –□ -, Day 1 Fed; –●–, Day 5 Fasting; –■–, Day 5 Fed)

Results

Subjects

Of the 47 subjects randomized, 44 completed the study (two withdrew consent, one had a positive urine screen for drugs of abuse). Approximately half of the subjects were men (53.2%), most were White (91.5%), mean age was 31.9 years (range 19–50 years) and the mean body mass index was 24.4 kg m^{-2} (range 18.8–28.4 kg m^{-2}). The number of subjects with sufficient data to calculate both AUC and C_{max} on days 1 and 5 were 35 and 43, respectively.

Pharmacokinetics

On days 1 and 5, C_{max} and AUC were lower when esomeprazole was administered under fed *vs.* fasting conditions; however, the effect of meal timing was not as great on day 5 as that observed on day 1 (Figure 1; Table 1). The 90% CIs for the ratio of fed *vs.* fasting AUC and C_{max} values were outside the range of 0.80–1.25 on days 1 and 5; therefore, the two regimens were not bioequivalent (Table 1). On days 1 and 5, t_{max} and $t_{1/2}$ values were longer under fed conditions (Table 1).

Discussion

The pharmacokinetic results of this study in fasting subjects are consistent with those of previous reports of the pharmacokinetics of esomeprazole administered under fasting conditions [9, 10]. In the present study of healthy volunteers, the results show that taking esomeprazole within 15 min of eating a high-fat, high-calorie meal reduced systemic drug exposure, although the reduction seemed less pronounced with repeated dosing.

Delayed gastric emptying can result in decreased absorption of the drug and, hence, lower AUC and C_{max} values [11]. Meals with a high fat content slow gastric emptying [12]. A high-fat meal, i.e. a common American breakfast, was chosen for this study to provide the greatest likelihood of detecting a food effect and to mimic a situation in which gastric emptying would be expected to be delayed [12]. The 15-min interval between esomeprazole administration and feeding was chosen to approximate patterns of real-life use by patients.

Inhibition of intragastric acid secretion by esomeprazole increases with higher exposure (AUC) [3]. Because a direct relationship exists between plasma AUC and the antisecretory effects of PPIs, it might be expected that administration of esomeprazole with food would decrease acid suppression [3, 4]. However, Junghard *et al.* [4] have found that food has no significant effect on the percentage of time that intragastric pH is >4.0, even though AUC and C_{max} are decreased. Furthermore, Junghard *et al.* [4] reported that the relative decrease in C_{max} was more pronounced than that of AUC; therefore, the plasma concentration profile was more extended/wider, indicating a longer duration with esomeprazole exposure, which may explain the lack of food effect on the percentage of time with pH > 4.0. Food activates proton pumps, which results in acid secretion, but also buffers gastric acid, which may increase the therapeutic effect of a PPI. The clinical effect of food may be a balance of all of these factors, and it is not possible to know definitively based on the results of this study.

The acid labile nature of esomeprazole may explain the decreased bioavailability. Under fed conditions, food delays gastric emptying (prolonged t_{max}) and esomeprazole degradation increases with increased time in the stomach. The increased bioavailability on day 5 *vs.* day 1 may be a result of reduced gastric acidity due to the antisecretory effect of esomeprazole and/or a decreased delay in gastric emptying on day 5 *vs.* day 1.

In conclusion, administration of food 15 min after dosing with esomeprazole reduces bioavailability on days 1 and 5 of dosing in healthy volunteers.

Competing interests: This study was conducted and funded by AstraZeneca LP, Wilmington, DE, USA; all authors are employees of AstraZeneca LP. The authors

Table 1
Pharmacokinetic parameters of esomeprazole 40 mg once daily in fed and fasting healthy adult volunteers

Parameter	Day 1 Fed	Day 1 Fasting	Day 1 Ratio*	Day 5 Fed	Day 5 Fasting	Day 5 Ratio*
AUC						
n	35	43	35	43	44	43
μmol h^{-1} l^{-1}	4.04 (3.2)	6.71 (4.3)	0.56 (0.50, 0.64)	9.47 (3.3)	12.31 (4.1)	0.78 (0.74, 0.82)
AUC_{0-t}						
n	44	44	NC	44	44	NC
μmol h^{-1} l^{-1}	2.80 (3.2)	6.66 (4.1)		9.22 (3.3)	12.22 (4.1)	
C_{max}						
n	44	44	35	44	44	43
μmol l^{-1}	0.88 (1.1)	3.48 (1.5)	0.34 (0.28, 0.41)	2.45 (1.4)	5.37 (1.4)	0.47 (0.41, 0.52)
t_{max}, h†						
n	44	44		44	44	
Median	4.02	2.00	–	2.50	1.50	–
Range	0.77–9.00	1.00–4.02		0.77–8.00	0.77–4.50	
$t_{1/2}$, h†						
n	37	44		43	44	
Mean	1.53	1.07	–	1.47	1.28	–
Range	0.59–4.10	0.55–2.05		0.90–4.30	0.85–1.73	

*Values shown are geometric means (SD) unless otherwise indicated. AUC, Area under the plasma concentration–time curve; AUC_{0-t}, area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration; CI, confidence interval; C_{max}, maximum plasma esomeprazole concentration; t_{max}, time to peak esomeprazole concentration; $t_{1/2}$, elimination half-life. *Ratio (90% CI) of fed to fasting calculated for those subjects with profiles from both periods. †Arithmetic mean (range) or median (range).*

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