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Esomeprazole administered through a nasogastric tube provides bioavailability similar to oral dosing

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SUMMARY

Aim: To determine if nasogastric tube administration of the enteric-coated pellets from an opened esomeprazole capsule provides bioavailability similar to oral dosing with the intact capsule.

Methods: A randomized, single-centre, open-label, two-period crossover pharmacokinetic study consisting of two 5-day dosing periods separated by a 7- to 14-day washout period was conducted. Healthy subjects between the ages of 18 and 50 years received esomeprazole 40 mg once daily either orally as an intact capsule, or as a suspension of the enteric-coated pellets from an opened capsule in water through a nasogastric tube.

Results: In 47 evaluable subjects, the 90% confidence intervals were 0.87–1.08 and 0.93–1.25 for the geometric mean of the ratio of nasogastric tube administration relative to administration of the intact capsule for the area under the plasma concentration–time curve and for maximum plasma concentration, respectively, on day 1, demonstrating bioequivalence. Oral and nasogastric administration also demonstrated similar bioavailabilities on day 5. Esomeprazole was well tolerated regardless of the mode of administration.

Conclusions: Nasogastric tube administration of the enteric-coated pellets from an opened esomeprazole 40 mg capsule provides bioavailability similar to oral dosing. Administration of the contents of an opened esomeprazole 40 mg capsule in water through a nasogastric tube is a practical alternative for patients with feeding tubes who require effective gastric acid suppression, but cannot swallow an oral preparation.

INTRODUCTION

Esomeprazole is the first proton-pump inhibitor to be developed as an optical isomer. In clinical trials, esomeprazole 40 mg once daily for up to 8 weeks was more effective than lansoprazole 30 mg or omeprazole 20 mg for healing and producing sustained resolution of heartburn in patients with reflux-associated erosive oesophagitis.[1–3] Esomeprazole 20 mg once daily maintains healing and symptom relief for 6 months in more patients than the FDA-approved maintenance dose of lansoprazole, 15 mg once daily.[4]

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Esomeprazole is currently available in the USA as a capsule containing enteric-coated pellets. For patients with difficulties swallowing the intact capsule, the pellets within the capsule can be administered mixed in one tablespoonful of apple sauce without affecting drug bioavailability.[5] For patients with feeding tubes in place, administration of the pellets from an opened capsule in water through the tube would be a practical method to provide acid suppression with esomeprazole. Esomeprazole pellets have a smaller diameter than either of the other two FDA-approved encapsulated proton-pump inhibitors (lansoprazole and omeprazole), and therefore may be especially well suited for nasogastric tube administration.[6]

In vitro studies have demonstrated that esomeprazole pellets suspended in water and administered through

a syringe into an 8- or 14-French nasogastric tube or 20-French gastrostomy tube delivers virtually the entire contents of the capsule (> 98%).[6, 7] The primary objective of our investigation was to determine if nasogastric tube administration of the enteric-coated pellets from an opened esomeprazole capsule was bioequivalent to oral dosing with the intact capsule in humans at day 1. Secondary objectives were to determine if these two dosing regimens were bioequivalent at day 5, and to assess their safety and tolerability.

MATERIALS AND METHODS

A randomized open-label, single-centre, two-period crossover pharmacokinetic study was conducted in healthy men and women. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and in compliance with Good Clinical Practice regulations and guidelines issued by the FDA. Written, informed consent was obtained from all subjects prior to participation.

Study participants

Sixty healthy men ($n = 30$) and women ($n = 30$) between the ages of 18 and 50 years, inclusive, participated in the study. The body weight of each subject could not be greater than 20% above or below ideal body weight for their height and frame. Females of childbearing potential were required to use an acceptable method of birth control. Other exclusion criteria included: use of an experimental drug or device within 30 days prior to the screening visit; blood donation within the 8 weeks preceding screening; a history of chronic disease; a history of sinus surgery or sinus pathology that could affect passage of a nasogastric tube; a history of gastrointestinal disease or surgery that may affect drug absorption; a history of multiple drug allergies or other drug-associated adverse events; a positive test for drugs of abuse; use of nicotine-containing products within 3 months of study commencement or during the study. Women who tested positive for pregnancy or were lactating were also excluded. Laboratory values outside the reference range that were judged to be clinically significant resulted in exclusion. Consumption of alcohol was prohibited within 48 h of the first dose of study drug until day 5 for each study period. Subjects could not use prescription medication within 14 days prior to study commencement, whereas use of 'over-the-counter' drugs including herbals, was restricted within 7 days of study entry. Participants could not consume more than four cups of caffeine-containing beverages per day. All medications, including 'over-the-counter' drugs, were prohibited during the entire study period, except for contraceptives, hormone replacement therapy and acetaminophen.

Subjects were screened 14 days prior to the first study day. Each subject underwent a complete medical history, a physical examination, and collection of blood and urine specimens for routine analysis, urine drug screen and serum pregnancy testing for women of childbearing potential.

Administration of esomeprazole

Esomeprazole 40 mg was administered on each of five consecutive mornings, 30 min prior to breakfast, after overnight fasting. Following randomization by a computer-generated randomization schedule, subjects received a single 40 mg dose of esomeprazole as either an intact capsule with 240 mL of water or as enteric-coated pellets from an opened capsule suspended in water and administered via a syringe through a 16-French Levin-type nasogastric tube.

For nasogastric tube administration, 50 mL of water were placed into a 60 cm^3 catheter tip syringe, then the pellets from an opened esomeprazole 40 mg capsule were emptied into it. The syringe was shaken vigorously for 15 s, and then attached to the nasogastric tube. The contents were injected over 30 s through the tube using constant, gentle, side-to-side shaking. Immediately thereafter, the syringe was filled with an additional 30 mL of water which was flushed through the nasogastric tube.

Following a 7- to 14-day washout phase, subjects were switched to the alternate mode of administration (Figure 1).

Pharmacokinetic evaluation

On days 1 and 5, venous blood samples were drawn 5 min pre-dose, then at 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10, and 12 h post-dose. All blood samples were collected in heparinized tubes and centrifuged. The plasma was stored frozen at −20 °C until analysis. The plasma concentrations

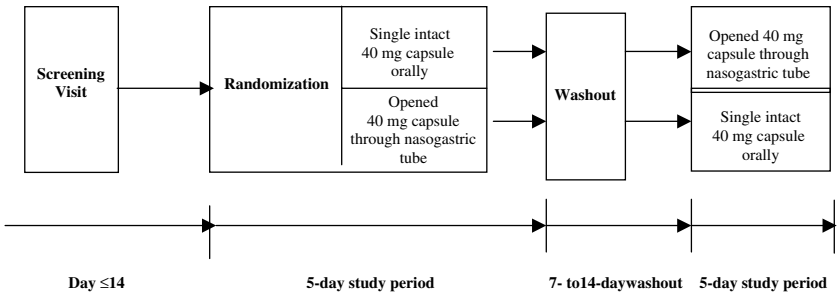

Figure 1. Study design.

of esomeprazole were determined at Quintiles AB (Uppsala, Sweden) using normal-phase liquid chromatography and ultraviolet detection. The limit of quantification was 25 nmol/L.

Pharmacokinetic parameters were estimated using a noncompartmental approach. The area under the plasma concentration–time curve (AUC) of esomeprazole was calculated by the trapezoidal method and extrapolated to infinity (on day 1) by adding the AUC from time zero to the time of the last quantifiable concentration to the residual AUC calculated as C_t/λ_z, where C_t is the last measured plasma concentration and λ_z is the terminal elimination rate constant. For day 5, the AUC was extrapolated to 24 h, representing one dose interval under multiple-dosing steady-state conditions. To calculate the AUC, an appropriate estimate of the terminal elimination rate constant was required from which the plasma concentration–time curve up to 24 h could be extrapolated. The elimination rate constant was determined by log–linear regression analysis of the terminal part of the plasma concentration vs. time curve. An estimate of the terminal elimination rate constant was considered appropriate when it was supported by at least two half-lives of plasma concentration–time data. The observed maximum plasma concentration (C_{max}) and time to maximum concentration (t_{max}) were recorded.

Statistical analysis

Subjects who had a C_{max} and calculable AUC for each mode of administration were considered evaluable for the pharmacokinetic analyses.[8] Logarithmic values for AUC and C_{max} were analysed using an analysis of variance model. Contrasts between regimens were calculated, and the results presented in terms of a geometric least-square (GLS) mean of the ratio of nasogastric tube vs. oral administration with its 90% confidence interval. Bioequivalence was concluded if the 90% confidence intervals fell within the range 0.80–1.25.

RESULTS

No subject withdrew from the study, and there were no major protocol deviations. Baseline demographic characteristics are presented in Table 1. The majority of the subjects were African American with nearly equal numbers of men and women. Of 60 randomized subjects, 47 provided evaluable data on day 1 and 55 provided evaluable data on day 5; the remaining subjects were not evaluable because their pharmacokinetic data were insufficient to calculate an AUC based on the pre-set criteria outlined under *Pharmacokinetic Evaluation.* These patients had much longer apparent terminal elimination rate constant estimates than could be supported by the data available. The mean esomeprazole plasma concentration vs. time profiles for nasogastric tube administration of the capsule contents and oral dosing with the intact capsule for days 1 and 5 are presented in Figure 2. The profiles of the two curves on both days were virtually superimposable.

Table 1. Baseline demographic characteristics

	Evaluable subjects	
	Day 1 ($n = 47$)	Day 5 ($n = 55$)
Gender		
Male, *n* (%)	23 (49)	28 (51)
Female, *n* (%)	24 (51)	27 (49)
Race		
White, *n* (%)	15 (32)	19 (34)
African American, *n* (%)	32 (68)	36 (66)
Age (years) mean (s.d.)	40.6 (5.3)	39.6 (6.5)

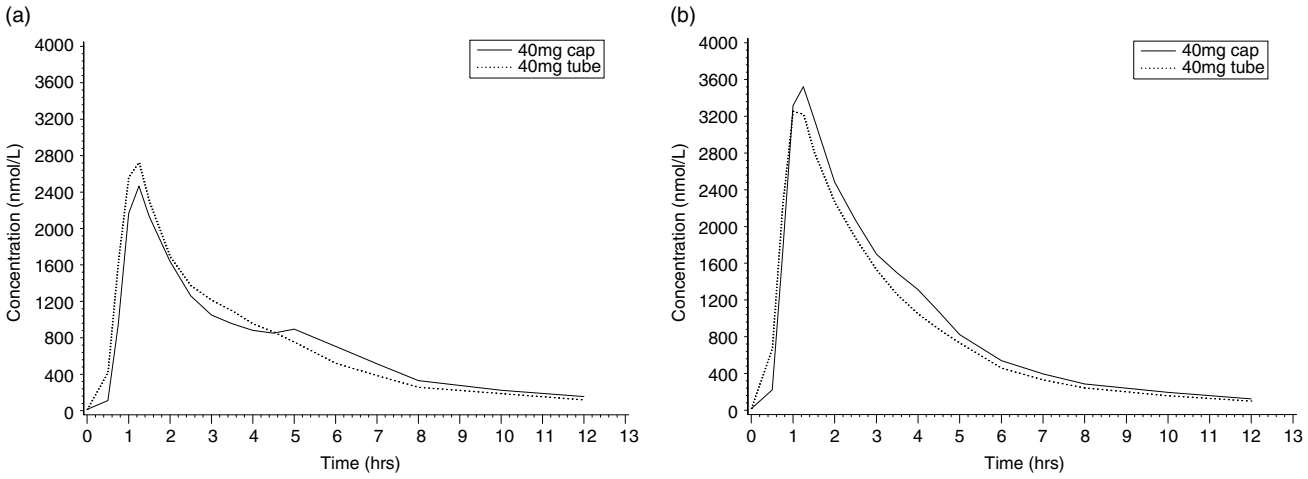

Figure 2. Mean plasma esomeprazole concentration vs. time profiles from 0 to 12 h for oral dosing with the intact capsule (cap), and nasogastric tube administration with the pellets from an opened capsule on day 5 (a) and day 1 (b).

Table 2. Mean pharmacokinetic parameters for nasogastric tube administration of the pellets from an opened capsule, and oral administration of the intact capsule at days 1 and 5

	AUC (μmol h/L)		C_{max} (μmol/L)		t_{max} (h)	
	NGT	Cap	NGT	Cap	NGT	Cap
Day 1 ($n = 47$)						
Median	7.88	8.00	3.72	3.44	1.3	1.3
Minimum	1.42	1.58	0.36	0.83	0.8	0.8
Maximum	41.28	37.46	11.38	8.89	6.0	6.0
Geometric mean	7.32	7.57	3.36	3.11	1.3	1.5
Day 5 ($n = 55$)						
Median	9.84	10.85	3.92	4.14	1.3	1.3
Minimum	0.86	4.12	0.54	1.72	0.8	0.8
Maximum	34.99	30.18	7.44	7.71	5.0	4.5
Geometric mean	9.30	10.59	3.73	4.25	1.3	1.3

AUC, Area under the plasma concentration–time curve; C_{max}, observed peak drug concentration; Cap, intact capsule; NGT, nasogastric tube; t_{max}, time to peak drug concentration.

Mean pharmacokinetic parameters for nasogastric tube administration and those for dosing with the intact esomeprazole capsule on days 1 and 5 are presented in Table 2. The mean AUC, C_{max} and t_{max} for nasogastric tube administration were similar to those of oral dosing with the intact capsule on days 1 and 5.

The bioequivalence data, expressed as ratios of the AUC and C_{max} on days 1 and 5 with 90% confidence intervals, are presented in Table 3. At day 1, nasogastric tube administration of the pellets from an opened esomeprazole 40 mg capsule was bioequivalent to oral dosing with the intact 40 mg capsule. At day 5, the two methods of administration demonstrated similar bioavailabilities.

Esomeprazole was well tolerated by the subjects regardless of the mode of administration. There were no serious adverse events or discontinuations due to an adverse event. Twenty subjects (33.3%) reported at least one adverse event during the study. Headache was the most common adverse event, reported by 8.3% of subjects following oral dosing with the intact capsule and 21.7% of subjects following nasogastric tube administration.

DISCUSSION

Nasogastric tube administration of the enteric-coated pellets from an opened esomeprazole 40 mg capsule is bioequivalent to oral dosing with the intact capsule on day 1. Oral and nasogastric administration demonstrate similar bioavailabilities on day 5, although the lower

Table 3. Mean ratios of pharmacokinetic parameters following once-daily administration of a 40 mg oral dose of esomeprazole through a nasogastric tube or as an intact capsule on days 1 and 5

	n	NGT/Cap* (90% confidence intervals)
Day 1		
AUC	47	0.97 (0.87–1.08)
C_{max}	47	1.08 (0.93–1.248)
Day 5		
AUC	55	0.88 (0.79–0.97)
C_{max}	55	0.88 (0.79–0.97)

AUC, Area under the plasma concentration–time curve; Cap, intact capsule; C_{max}, peak drug concentration; NGT, nasogastric tube.
* Geometric least-square mean of the ratio.

levels (0.79) of the 90% confidence intervals for the AUC and C_{max} fall just outside the range of bioequivalence.

In previous studies it has been demonstrated that the pellets from an opened esomeprazole capsule suspended in water can be efficiently delivered through a nasogastric tube *in vitro*.[6] Moreover, esomeprazole pellets remain stable after suspension in tap water and other beverages for up to 30 min[9]. Thus, our study supports the conclusions of these earlier reports and extends the results to assure that in patients who have feeding tubes and require gastric acid suppression, the contents of an esomeprazole capsule can be administered through a nasogastric tube and the pharmacokinetics will be similar to those following administration of the intact capsule.

Delivery of the contents of an opened capsule of other proton-pump inhibitors (omeprazole and lansoprazole) in water through a nasogastric tube has been highly variable because of adherence of the pellets to the tubing or cup.[10, 11] To circumvent these difficulties, either higher doses of these agents were administered, or recommended doses were injected very slowly over a 3–5 min period, or tediously, 6–10 granules at a time, through a feeding tube.[12–14] With esomeprazole, all of the pellets from the recommended dose capsule can be suspended in 50 mL of water and efficiently injected through a feeding tube within 30 s. It is recommended to flush the syringe and tube once with an additional 30 mL of water to assure more complete delivery. The individual esomeprazole pellets are smaller than those of omeprazole or lansoprazole,[6] which is likely to facilitate their efficient passage through the tube.

Nasogastric tube administration of esomeprazole pellets appeared to be associated with a numerically higher frequency of headache as an adverse event relative to oral dosing with the intact capsule. In previous studies in which esomeprazole pellets were given orally mixed with apple sauce to human volunteers, esomeprazole was well tolerated with no evidence of an increased incidence of headache.[5]

In conclusion, nasogastric tube administration of the enteric-coated pellets from an opened esomeprazole 40 mg capsule assures complete delivery of drug because the values of the AUC and C_{max} were similar to those after oral dosing with the intact capsule. The method used to administer esomeprazole is neither tedious nor time-consuming, and offers more convenience compared with previously described methods of nasogastric tube delivery using other proton-pump inhibitors. Administration of esomeprazole through a nasogastric tube is a practical option for patients with feeding tubes who require effective gastric acid suppression but cannot swallow an oral preparation. Moreover, it may provide a reasonable alternative to parenteral administration of proton-pump inhibitors for patients with functional gastrointestinal tracts.

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