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Gastric acidity and acid breakthrough with twice-daily omeprazole or lansoprazole

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SUMMARY

Background: In patients with severe gastro-oesophageal reflux disease (GERD), proton pump inhibitors are being used increasingly in twice-daily regimens to improve control of gastric acidity. Few data exist to compare the ability of the most-often used proton pump inhibitors, omeprazole and lansoprazole, to control gastric acid at twice-daily dosage regimens. Nocturnal acid breakthrough, defined as gastric pH < 4.0 continuously for > 60 min, may compromise treatment goals in patients with GERD.

Aim: To compare the effects of omeprazole 20 mg b.d. or lansoprazole 30 mg b.d. on gastric acidity and the relative ability of each dosage regimen to prevent acid breakthrough.

Methods: In a crossover pharmacodynamic study, 20 healthy volunteers (10 male, 10 female, mean age 38 years) were given omeprazole 20 mg b.d. or lansoprazole 30 mg b.d. for 7 days each, in a randomized manner. Each dosage regimen was separated by a minimum 7-day period where no medication was administered. On day 7 of each regimen, 24-h intragastric pH-metry was performed. The percentage of time for which gastric pH was below 4.0 and 3.0, the occurrence of daytime and nocturnal acid breakthrough, and the duration of action of each regimen were compared. Non-parametric statistics for paired data were used.

Results: The percentage time for which gastric pH was below 4.0 was significantly lower with omeprazole 20 mg b.d. (median 14.8%) than with lansoprazole 30 mg b.d. (median 24.2; $P = 0.0372$). Fourteen subjects showed more effective acid control when taking omeprazole; these were significantly more often *H. pylori*-negative patients compared with those for whom acid control was better on lansoprazole ($P < 0.001$). Nocturnal acid breakthrough occurred in seven patients (35%) on omeprazole and in 10 (50%) on lansoprazole (N.S.).

Conclusion: In healthy volunteers, twice-daily dosing of omeprazole 20 mg b.d. appears to be significantly more effective than lansoprazole 30 mg b.d. in controlling gastric acidity. The clinical importance of such a difference remains to be defined in GERD patients.

INTRODUCTION

In patients with gastro-oesophageal reflux disease (GERD), dysfunction of the anti-reflux barrier allows gastric contents to reflux into the oesophagus, oral cavity or sometimes the airway mucosa. As a result, the pH in these areas may approach that of the gastric contents, triggering troubling symptoms and creating mucosal lesions.

The primary medical treatment for GERD is the control of gastric acidity because abatement of symptoms and healing of mucosal lesions has been statistically correlated to maintaining gastric pH above 4.0 for 20 h or more of the 24-h period.[1] To date, the most effective suppression of gastric acidity has been obtained through

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the use of proton pump inhibitors. These are a group of drugs that act on the H^+, K^+ ATPase molecule, the so-called acid pump of the parietal cell, to inhibit acid secretion non-competitively.

Single daily doses of proton pump inhibitors appear to be comparable in clinical efficacy, however some patients may require increased doses to control their symptoms and heal their lesions.[2] In this group, twice-daily dosing is recommended to improve gastric acid control. It has been observed that there is considerable interindividual variation in the acid suppressive effects of these drugs. In addition, nocturnal gastric acid breakthrough, defined as 1 h or more where intragastric pH is continuously below 4, with accompanying acid reflux, occurs frequently in patients with GERD.[3, 4] The clinical importance of acid breakthrough in the production of nocturnal symptoms or erosive oesophagitis is unknown.

There are few data comparing the effectiveness of the two most widely used proton pump inhibitors, omeprazole and lansoprazole, in twice-daily dosing regimens. This study was designed to investigate the relative efficacy of each of these agents in controlling gastric acidity and acid breakthrough.

SUBJECTS AND METHODS

General design

This study was a two-way crossover pharmacodynamic study in normal volunteers. Each subject was studied with 24-h intragastric pH-metry at two points: on day 7 of a course of omeprazole 20 mg b.d., and on day 7 of a course of lansoprazole 30 mg b.d.[1, 2] The drugs were administered openly and in a randomized order. A washout period where no medication was administered, lasting for 1–4 weeks, was inserted between each test period of medication.

Study subjects

Participants were volunteers recruited amongst employees at a university hospital. Entry criteria required that they had only infrequent dyspeptic symptoms and used no medication on a constant basis. No medication was permitted during the study period. Endoscopy was not performed, but a serological test (FlexSure HP, SmithKline Diagnostics Inc., San Jose, CA) was conducted to establish *Helicobacter pylori* infection status.

Study medication

Medication was given openly as capsules of omeprazole 20 mg (Astra-Zeneca Inc., Wilmington, DE) or lansoprazole 30 mg (TAP Pharmaceuticals Inc., Deerfield, IL) 15 min before breakfast and dinner (b.d.). The study subjects were instructed to take the capsules with at least half a glass of water (75 mL). Compliance with medication was monitored using a diary.

Manometry

A manometric examination of the lower oesophageal sphincter served as a guide to correct placement of the pH-sensitive probe. Manometry was performed with a 5-channel solid-state catheter (Koenigsberg Inc., Pasadena, CA), with a station pull-through method.[5] The proximal border of the lower oesophageal sphincter was defined by the pressure inversion point just distal to the stable oesophageal baseline.[6]

Twenty-four hour pH-metry

A 2.1-mm catheter (Synectics Inc., Minneapolis, MN) with a monocrystalline antimony electrode directed laterally, 5 mm from the tip, and a separate skin reference electrode, were calibrated prior to each recording as per the recommendations of the manufacturer. Calibrations were made in buffers of pH 1.07 and 7.01 at room temperature, and an adjustment for body temperature was introduced.

The probe was passed trans-nasally and swallowed with a minimal amount of water. The pH catheter was then passed to the distal stomach and retracted to the estimated position, with its tip 15.0 cm distal to the upper margin of the lower oesophageal sphincter, as identified manometrically. It was thereby located in the proximal stomach, about 5–7 cm distal to the cardia, in the fundic or upper body region. The sampling rate was 0.25 Hz and recorded data were stored in a multichannel solid-state datalogger (Digitrapper Mark III, Synectics Inc.).

Recordings started in the morning and continued for 24 h. The subjects were allowed to return to work and follow their daily routine. They were instructed to take meals at 08.00 hours, 12.00 hours and 18.00 hours, with a composition and calorie content they were accustomed to, and to repeat this on each pH recording day. A diary was kept recording the exact timing and

composition of meals, and the time spent in recumbent position. Acid and alcoholic beverages were not allowed. The daytime period was defined from 06.00 hours until 22.00 hours. The nocturnal period was defined as the period between 22.00 hours and 06.00 hours, a period when the subject was asked to be recumbent.

At the end of the recording, data were edited in a dedicated software program (EsopHogram release 5.70, Gastrosoft Inc., Irving, TX). The percentage of the recording period for which gastric pH was less than 4.0, was calculated. Acid breakthrough was defined as periods when gastric pH was less than 4.0, continuously, for 60 min or longer. The occurrence of daytime or nocturnal acid breakthrough, and the time from drug intake in the morning or evening until the first episode of acid breakthrough occurred, were recorded.

Statistics

All comparisons were made using non-parametric statistics to reflect the commonly skewed distribution of gastric pH variables. The percentage of the total, daytime, and nocturnal period, for which gastric pH was less than 4.0 and 3.0 on the two regimens, was compared using a Wilcoxon matched pairs test. The proportion of subjects with nocturnal acid breakthrough on each regimen was compared using a χ^2-test. A P-value of < 0.05 was considered to indicate statistical significance.

RESULTS

Twenty healthy volunteers (10 male, 10 female), were recruited and started study medication. The mean age was 38 years (range 22–60 years). Five subjects were *H. pylori*-positive, 15 were negative. Omeprazole 20 mg b.d. was administered to 10 subjects first whilst lansoprazole 30 mg b.d. was administered to the other 10 subjects first. There were no significant differences in results according to the sequence of medication.

The percentage of total time for which gastric pH was below 4.0 was significantly lower in the omeprazole study subjects (median 14.8%, interquartile range 3.2–30) than in the lansoprazole 30 mg b.d. study subjects (median 24.2%, interquartile range 10.5–40.1) ($P = 0.0377$). These data are shown in Figures 1 and 2. Data for the total period, daytime

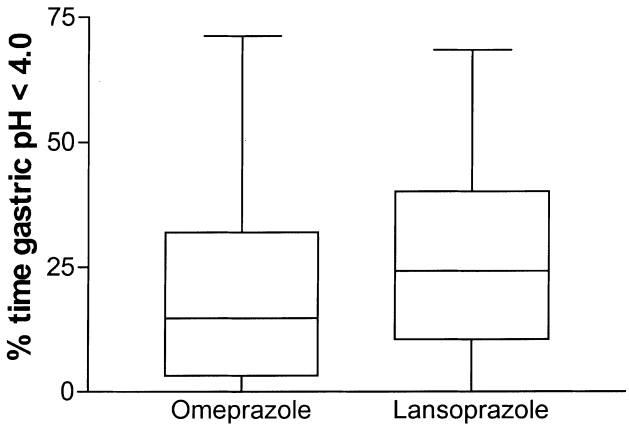

Figure 1. Per cent time for which gastric pH was maintained at less than 4.0 in 20 volunteers who took omeprazole 20 mg b.d. or lansoprazole 30 mg b.d. for seven days each in an open crossover pharmacodynamic study. In this box-and-whiskers plot the median value is indicated as the transverse line within the box, the interquartile range as the vertical extent of the box, and the total range as the whiskers. The omeprazole regimen was significantly more effective than lansoprazole ($P < 0.0377$).

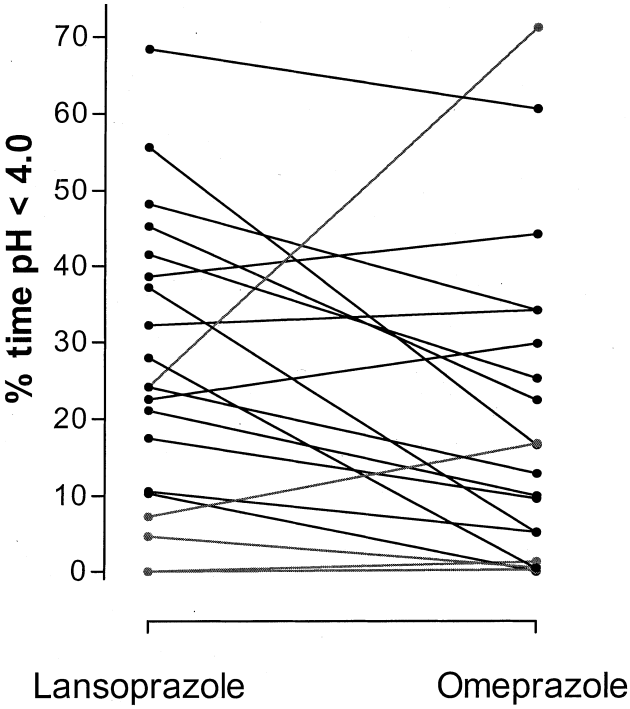

Figure 2. This illustrates the individual pH data on the percentage time for which gastric pH was maintained at less than 4.0 in the volunteers studied. Of particular note there is the wide intersubject variability in control of intragastric pH with both drugs.

Table 1. Parameters of gastric acidity recorded in 20 volunteers who received omeprazole 20 mg or lansoprazole 30 mg before breakfast and dinner

	Omeprazole	Lansoprazole
Total period:		
% time pH < 4.0	14.8	24.2 $P = 0.0377$
-IQR	3.2–32.0	10.5–40.1
% time pH < 3.0	8.1	18.1 $P = 0.0799$
-IQR	1.8–25.0	5.2–30.0
Daytime period:		
% time pH < 4.0	14.3	21.6 $P = 0.1285$
-IQR	1.4–25.4	10.3–32.3
Night-time period:		
% time pH < 4.0	18.2	27.4 $P = 0.1516$
-IQR	1.6–40.1	19.1–53.7

and night-time periods, including interquartile ranges, are depicted in Table 1. Fourteen subjects had greater acid control with omeprazole, while five had greater acid control with lansoprazole. In general intersubject variability in pH control was quite large with either drug, while intrasubject variability was less striking (Figure 2). One subject differed markedly from the others, showing average acid control when taking lansoprazole, but much less control when taking omeprazole (percentage time gastric pH < 4 of 24.2 vs. 71.2%). In the 14 subjects in whom pH control was superior with omeprazole, *H. pylori* serology was negative in 13 of them, while four out of five subjects with superior control on lansoprazole had positive *H. pylori* serology. The sample size does not allow any definite clinical conclusions to be drawn from this difference.

Nocturnal acid breakthrough occurred in seven (35%) omeprazole subjects and 10 (50%) lansoprazole subjects ($P = 0.4$). Daytime acid breakthrough (longer than 1 hour drop in pH < 4) was seen in four (20%) and nine (45%) subjects, respectively. The 25 percentile value for duration of action of omeprazole was > 660 min for the morning dose and 416 min for the evening dose. While the duration of action for lansoprazole was somewhat shorter (531 min and 296 min, respectively), these differences were not statistically significant. One subject differed markedly from the others, showing average acid control when taking lansoprazole, but much less control when taking omeprazole (percentage time gastric pH < 4 of 24.2 vs. 71.2%).

DISCUSSION

The present study confirms our previous observation that proton pump inhibitors, even with twice-daily dosing, do not control gastric acidity throughout 24 h in many subjects. This is the case with either omeprazole 20 mg b.d. or lansoprazole 30 mg b.d. Most often, these drugs fail to control nocturnal gastric pH.

Nocturnal acid breakthrough is seen in 70% of GERD patients on proton pump inhibitors b.d., and is associated with gastro-oesophageal reflux in 30–50% of patients.[3, 4] Among patients with acid peptic disorders, omeprazole has traditionally been prescribed once daily. Patients with reflux oesophagitis may require greater suppression of gastric acid, in order for lesions to heal, than patients with peptic ulcer disease. This may be particularly true in patients with nocturnal gastro-oesophageal reflux.

Omeprazole 40 mg daily has been shown to be more effective in some studies than 20 mg daily, in achieving healing and symptom relief, and may be considered a standard dose in patients with severe or complicated GERD.[7] It has been shown that gastric acid control with omeprazole 40 mg once daily (o.m.) can be significantly improved when the dose is divided (20 mg b.d. taken before breakfast and dinner).[8] This dosage regimen has also been shown to significantly improve nocturnal acid control.[9]

Although the numerical differences in gastric acid control between the two therapies tested in this study were relatively small, omeprazole was more effective than lansoprazole in most study subjects, and this difference was statistically significant. In some individuals, the difference was as high as 40% of 24 h, which strongly suggests that it may be of clinical importance.

Both drugs controlled daytime gastric acidity better than night-time acidity. The difference in percentage time for which gastric pH was below 4.0, observed between omeprazole and lansoprazole, were relatively similar during the day and night, but due to the limited number of patients and higher variability during shorter recording periods, differences were not statistically significant. There was no significant difference between the two drugs in the occurrence of nocturnal gastric acid breakthrough. The duration of action, which was defined as time from drug intake until acid breakthrough occurred, was similar, and no significant differences were seen. This parameter was difficult to study because no more than 35–50% of subjects had acid breakthrough.

Day-to-day variation in gastric acid control in subjects on chronic acid suppressive medication has not been extensively studied. Nonetheless, gastric pH-metry performed in the gastric body is thought to be highly reproducible.[10] Under the relatively well-controlled conditions of the present study, we observed considerable intrasubject variation in effect between the two drugs, as shown in Figure 1. The reason for this is unknown and requires further study, but suggests that in patients in whom 24 h pH control is inadequate to control symptoms on one proton pump inhibitor, a change in proton pump inhibitor might be considered.

Several studies of gastric acidity in volunteers taking omeprazole or lansoprazole once daily have been performed and some have shown lansoprazole 30 mg to be either as effective as, or significantly more effective than, omeprazole 20 mg.[11, 13–15] Recent data indicate that dosing of omeprazole and lansoprazole in relation to meals is important to obtain maximal gastric acid suppression.[16] For lansoprazole, however, an important pharmacokinetic interaction with antacids and food, resulting in decreased bioavailability, has been reported.[17] Omeprazole is more susceptible to acid degradation, which favours intake with food to increase bioavailability. Since the evening dose in our study was given in relation to dinner, the largest meal, this may explain the superior effect of omeprazole on gastric acidity. More pronounced meal interaction for lansoprazole and more acid degradability for omeprazole may have both contributed towards a relatively better effect of omeprazole. Dosing prior to a big meal such as dinner may be important.

Although the number of subjects is quite small, there was a difference in response to the two drugs according to *H. pylori* serology status, with lansoprazole appearing to be more effective in *H. pylori*-positive subjects. It is well known that the antisecretory response to proton pump inhibitors is significantly better in subjects with *H. pylori* associated gastritis. If previously published studies were performed in subjects who were predominantly *H. pylori*-positive, this may explain why lansoprazole has been as effective or more effective than omeprazole. Our findings are in contrast to those of Verdù and co-workers, who compared omeprazole 20 mg and lansoprazole 30 mg o.d. in *H. pylori*-positive healthy volunteers and found no significant difference in median 24 h gastric pH between the two groups.[18] They observed a slightly better effect of omeprazole during the day and of lansoprazole during the night. We have found a difference in overnight control of intragastric pH in *H. pylori*-positive, compared with *H. pylori*-negative subjects, in a dose ranging study with pantoprazole; Van Herwaarden *et al.* recently found that lansoprazole exhibited a significantly decreased 24 h intragastric pH contol in *H. pylori*-positive normal subjects when re-tested with intragastric pH monitoring after successful eradication.[19, 20] As we measured quantitative serology only and did not perform biopsies to assess the presence or absence of gastritits we cannot make definite comments about the effect of *H. pylori* infection on the differences between these two drugs. However, the above findings, coupled with those in this study, suggest that *H. pylori* status affects intragastric pH control on proton pump inhibitors. While we cannot explain the mechanism by which this occurs, these data are provocative and require further study. Since plasma drug concentrations were not measured in the present study, there is no information regarding pharmacokinetic differences between *H. pylori*-positive and negative subjects. A previous study showed important differences in pharmacokinetic parameters for lansoprazole among patients with GERD vs. healthy volunteers;[21] these differences that may have been due to differences in age and/or *H. pylori* infection status.

We observed one subject in this study who had average acid control with lansoprazole, but very poor effect with omeprazole. This effect was comparable to that of placebo, administered in a previous study in which he also took part. This other study showed him to be also relatively resistant to the effect of pantoprazole 10–40 mg daily. We have previously published our experience with patients who show resistance to omeprazole, defined as maintaining a pH < 4 for > 50% of 24 h when taking omeprazole 20 mg b.d., and also reported that in these selected patients, lansoprazole is significantly more effective in keeping overnight gastric pH > 3.[22, 23]

A clear relationship between intragastric pH control and healing or symptom relief has not been carefully assessed; in particular the clinical importance of the differences found in this study, in terms of symptom improvement and healing rates for patients with GERD, is unknown. As the number of volunteers studied was small, other significant differences in intragastric pH control between the drugs, particularly overnight, may not have been discovered. Given the importance of maximal acid control to achieve successful treatment in refractory reflux, there may be a sub-group of GERD

patients for whom this small difference is important. However, these observations must be tested in appropriate patients before clinical conclusions can be drawn. The relationship of *H. pylori* status to dosing efficacy is intriguing and warrants further study in subjects and patients, in whom *H. pylori* infection status is more rigorously assessed.

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