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Proton pump inhibitors: better acid suppression when taken before a meal than without a meal

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SUMMARY

Background: Proton pump inhibitors including omeprazole and lansoprazole inhibit gastric acid secretion by selectively and non-competitively inactivating the H^+, K^+ ATPase molecules of the parietal cell, but possibly only those that are actively secreting acid. This might imply that stimulation of acid secretion by a meal is necessary for optimal inhibition of gastric secretion.
Aim: To quantify and compare the effect on daytime gastric acidity of omeprazole 20 mg or lansoprazole 30 mg daily taken 15 min before breakfast, with that of the same drug taken without a meal.
Methods: Twenty-one healthy volunteers were randomized to receive either omeprazole or lansoprazole. They were given the drug for two separate periods of 7 days in randomized order and at least 7 days apart. During one period the study medication was taken before breakfast; during the other it was taken at the same hour, but with no meal until 12:00 hours. Lunch was standardized. On day 7, intragastric pH-metry was performed, starting at 08:00 hours. Tracings were analysed for the 8-h period from 08:00 hours until 16:00 hours with regard to percentage time for which gastric pH was below 4.0 and 3.0, and median gastric pH. Tracings were also analysed after removing the 1 h breakfast period, to exclude the buffering effect of the meal.
Results: When taking the drug with breakfast, the median percentage time for which gastric pH < 4.0 was 17.2 (interquartile range 4.6–45.5), compared with 42.0 (interquartile range 31.4–48.8) when taken without food ($P = 0.01$). Fifteen subjects had better control of gastric acidity when the medication was taken with breakfast. A pH threshold of 3 and median pH showed similar differences. When the breakfast period was removed, the differences were no longer statistically significant.
Conclusions: When therapy with omeprazole or lansoprazole is indicated, medication should be taken before a meal for optimal control of daytime gastric acidity.

INTRODUCTION

The primary method to control symptoms of gastro-oesophageal reflux disease (GERD) is suppression of gastric acidity. Healing of reflux oesophagitis with antisecretory medication is statistically correlated to the percentage of the 24-h period for which gastric pH is maintained above 4.0.[1]

Traditionally, H_2-receptor antagonists have been used in the treatment of mild to moderate reflux disease, but food intake interferes with the effect of these drugs at two levels: decreased absorption and inability to suppress meal-induced acid secretion.[2] Studies of intragastric acidity in patients being treated with proton pump inhibitors have shown significantly better control of gastric acidity, but in a sub-group of patients, acid suppression is insufficient to achieve healing and symptom relief.[3, 4]

Proton pump inhibitors including omeprazole and lansoprazole inhibit gastric acid secretion by selectively and non-competitively inactivating the H^+, K^+ ATPase molecules of the parietal cell. Optimal antisecretory effect occurs when the proton pumps are activated as

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the parietal cell is maximally stimulated as it is after a meal. Therefore, intake of medication in relation to meals may be important to optimize their effect and avoid therapeutic failure. Proton pump inhibitors are most often prescribed for intake in the morning, but there are many people who do not take the time to have breakfast. Thus they take their proton pump inhibitor without optimal parietal cell turnover, perhaps decreasing efficacy. The present study was designed to document this effect and to quantify and compare the effect of these drugs on daytime intragastric acidity when taken with or without breakfast.

SUBJECTS AND METHODS

Study subjects were healthy volunteers recruited amongst employees in a university hospital. They were required to have no more than infrequent dyspeptic symptoms and to use no medication on a constant basis and, in particular, no medication whatsoever during the study period.

General design

The study was a crossover pharmacodynamic study. Each subject was randomized to receive either omeprazole or lansoprazole. This drug was taken for two isolated periods of 7 days, one during which medication was taken with breakfast and one without eating, in randomized order. On day seven of each period, a 9-h intragastric pH-metry was performed. A washout period with no medication, of 1–4 weeks, was inserted between each period of medication.

Study medication

Medication was given as one capsule of omeprazole 20 mg (Astra-Zeneca, Wayne, PA) or lansoprazole 30 mg (TAP Pharmaceuticals Inc., Deerfield, IL) before breakfast for 7 days. The study subjects were instructed to take the capsules with at least half a glass of water (75 mL). Medication was given openly and compliance was monitored with a diary. Subjects took medication on their own on non-study days.

Meals

During both study weeks, medication was taken at the same time in the morning. During one of the weeks, it was taken 15 min before a breakfast meal, which was required to be close to the subject's ordinary breakfast, in calorie content, and to include milk or yoghurt, coffee or tea, and bread or a muffin. A diary was kept to ensure that a daily breakfast was eaten. During the other week, the medication was taken without any food or drink except for water, until noon. Lunch was standardized for all study subjects and included a turkey and cheese sandwich and a 563-mL bottle of a soda drink at 13:00 hours.

Manometry

A manometric examination of the lower oesophageal sphincter was carried out initially to serve as a guide to correct placement of the pH-sensitive probe. A 5-channel solid-state catheter (Konigsberg Instruments Inc., Pasadena, CA) and a station pull-through method was used.[5] The proximal border of the lower oesophageal sphincter was defined by the pressure inversion point, just distal to the stable oesophageal baseline.[6]

24-h intragastric pH-metry

A 2.1-mm catheter (Synectics Inc., Minneapolis, MN) with a monocrystalline antimony electrode 5 mm from the tip, and a separate skin reference electrode were used. The electrode was calibrated prior to each recording as recommended by the manufacturer, 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 passed to the distal stomach, and retracted to the estimated position, with the electrode located in the proximal stomach, 15 cm distal to the upper border of the lower oesophageal sphincter. 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 lasted for 8–9 h. The subjects were instructed to take meals at 08:00 hours and 13:00 hours exactly. Alcoholic beverages were forbidden as was time spent in the recumbent position. The pH probe was placed a 07:30 hours on the study day.

At the end of the recording, digital values were transferred to an IBM compatible computer for processing and editing in a dedicated software program

(EsopHogram release 5.70, Gastrosoft Inc., Irving, TX). The primary parameter calculated from the gastric recordings was the percentage of the total recording period for which gastric pH was less than 4.0. Secondary parameters were: percentage time gastric pH less than 3.0 and median gastric pH. Percentage time gastric pH < 4.0 was also analysed after having removed the time interval of the recordings corresponding to the time during which the subject had breakfast (approximately 15 min) and a 45-min postprandial period thereafter.

Statistics

All comparisons were made using non-parametric statistics to reflect the commonly skewed distribution of gastric pH variables. The percentage of time when gastric pH was less than 4.0 or 3.0, as well as median gastric pH when the drug was taken with or without breakfast, were compared using a Wilcoxon matched pair's test. Differences between the groups on each drug and the order of taking the drug with or without breakfast was compared, using a Mann–Whitney test, before pooling the data. A *P*-value of < 0.05 was considered to indicate statistical significance.

RESULTS

Twenty-one healthy volunteers (10 females, 11 males) were recruited and started study medication. The mean age was 37 years (range 21–62 years). No significant differences were seen between subjects taking omeprazole ($n = 10$) or lansoprazole ($n = 11$), nor between subjects having taken the drug with ($n = 11$) or without ($n = 10$) breakfast first; data were therefore pooled.

The percentage of the 8-h recording period for which pH was less than 4.0 are shown in Figure 1 and Table 1. The median value for pooled data with both agents was 17.2% when taking medication with breakfast compared with 42.0% when taking it without food ($P = 0.01$). Other variables of gastric acidity including median percentage of the recording period for which gastric pH was less than 3.0 are shown in Table 1. Fifteen subjects had better control of gastric acidity when the medication was taken with breakfast. There was a marked degree of inter-subject variability in acid control, as can be seen from Figure 2. The median time for which intragastric pH < 4 for lansoprazole was 14.2% with food and 48.1% without; for omeprazole, 20.1% with food and 31.4% without. (Figure 3).

The median percentage time for which gastric pH < 4.0 during the recording when the breakfast period was removed was 19.0 when taking medication with breakfast, compared to 28.6 when taking it without breakfast ($P = 0.17$).

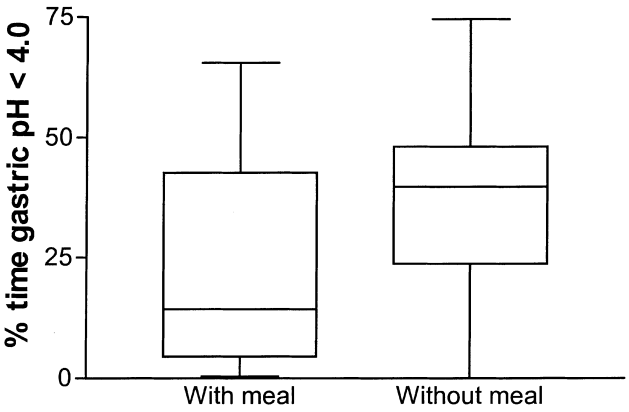

Figure 1. Percentage time for which gastric pH < 4.0 during 8 h on day 7 in 21 volunteers taking a proton pump inhibitor (either omeprazole 20 mg or lansoprazole 30 mg) each morning, either 15 min before a breakfast meal or without food or drink (except for water), until 12 noon. In this box-and-whiskers plot the median values are indicated as the transverse line within the box, the interquartile range as the vertical extent of the box and total range as the whiskers. Acid suppression was significantly more effective when medication was taken with breakfast than without ($P < 0.01$).

Table 1. Parameters of gastric acidity in 21 volunteers taking a proton pump inhibitor (omeprazole 20 mg or lansoprazole 30 mg) either 15 min before breakfast or without food or drink (except for water), until 12 noon. Data are given as median values and interquartile range (IQR)

	Without breakfast	With breakfast	*P*
Total 9-h period			
% time pH < 4.0	42.0	17.2	0.01
IQR	31.4–48.8	4.6–45.5	
% time pH < 3.0	27.5	14.4	0.01
IQR	11.2–41.9	2.4–28.0	
Median gastric pH	5.1	6.0	0.05
IQR	4.2–5.8	4.8–6.3	
Breakfast period removed			
% time pH < 4.0	28.6	19.0	0.17

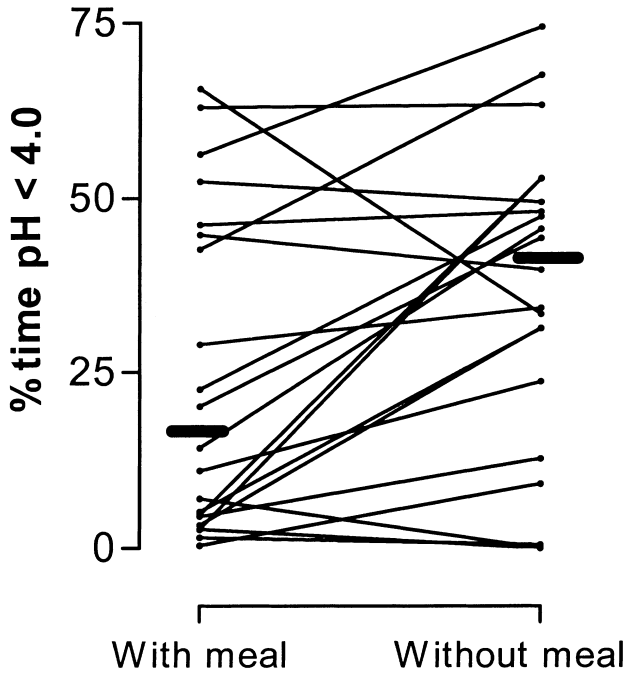

Figure 2. Individual data on the percentage time for which gastric pH < 4.0 during 8 h on day 7 in 21 volunteers taking a proton pump inhibitor (omeprazole 20 mg or lansoprazole 30 mg) each morning, either 15 min before a breakfast meal or without food or drink (except for water), until 12 noon. Acid suppression was significantly more effective when medication was taken with breakfast than without ($P < 0.01$). Note the marked inter-subject variability in acid suppression.

DISCUSSION

Lansoprazole and omeprazole are potent suppressors of gastric acid secretion.[7] Their plasma half-life is short, on the order of 0.6–2 h. Their pro-drugs are trapped and activated in the acid milieu of the secretory canaliculi of gastric parietal cells and are covalently bonded to Cys 823 on the alpha subunit of the H^+, K^+ ATPase molecule, the acid-secreting molecule of the parietal cell surface, thereby inactivating it.

The H^+, K^+ ATPase molecule is synthesized within the endoplasmic reticulum of the parietal cell and is stored in the vesicles of the Golgi apparatus, until carried to the apical surface of the cell in response to functional stimulation. Proton pump inhibitors may block only molecules that are present on the surface, while inactive molecules within the cell may escape inhibition and be recruited to the surface as a response to later stimulation of the cell. A large pool of uninhibited molecules are likely to limit the effectiveness and duration of action of proton pump inhibitors.

Traditionally, patients have been advised to take omeprazole and lansoprazole in the fasting state in the morning. Most patients with GERD have abnormal daytime, often postprandial, gastro-oesophageal reflux, which is, therefore, important to control. The bioavailability of a morning dose of omeprazole is significantly higher than that of an evening dose, when taken in the fasting state.[8] The bioavailability of omeprazole seems relatively unaffected by food intake, although absorption is delayed.[9] With lansoprazole it has been shown that intake in the fasting state results in

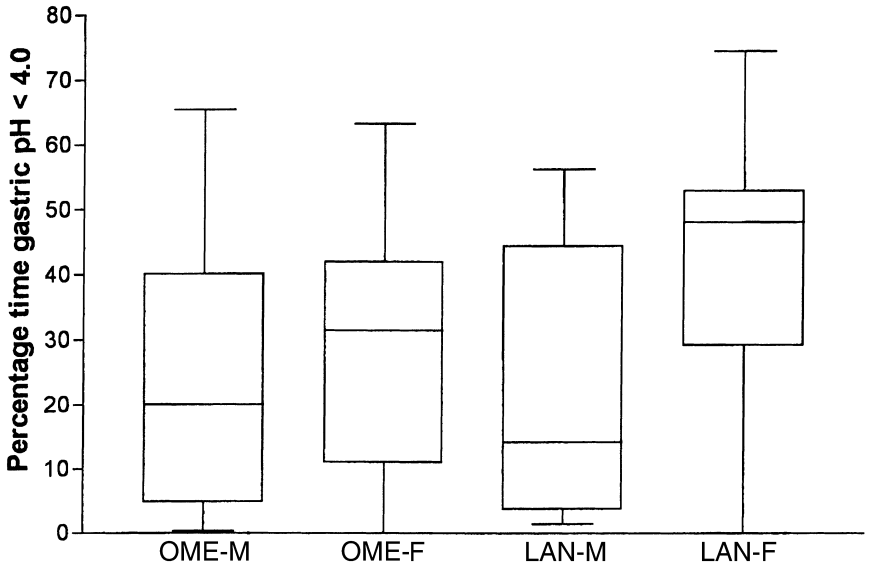

Figure 3. Percentage time for which gastric pH < 4.0 on day 7 in volunteers taking either omeprazole 20 mg ($n = 10$) or lansoprazole 30 mg ($n = 11$) each morning for two separate periods. During one period medication was taken 15 min before a breakfast meal (OME-M and LAN-M groups), during the other it was taken floating (except for water), until 12 noon (OME-F and LAN-F groups). In this box-and-whiskers plot the median values are indicated as the transverse line within the box, the interquartile range as the vertical extent of the box and total range as the whiskers. No differences observed were statistically significant.

significantly higher systemic bioavailability and peak plasma concentrations of the drug than intake during or after breakfast.[10, 11] In one study, intake of omeprazole with breakfast resulted in significantly higher gastric pH throughout 24 h, than intake in the evening fasting.[12]

Several studies have investigated the effect of the time relationship between drug and meal intake. A recent study with omeprazole showed that intake with breakfast or dinner were equivalent, in terms of the percentage time for which gastric pH > 4 over 24 h.[13] No difference in the total time for which gastric pH > 3 was found between taking lansoprazole 30 min before breakfast or 30 min after the meal.[14] The discrepancy between lower bioavailability and the better effect on gastric acidity suggests some additional effect induced by the meal.

It was our working hypothesis that the intake of a proton pump inhibitor in close relation to a meal is necessary to achieve optimal inhibition of acid secretion. Several factors may influence the resulting gastric acidity in this situation: intake with a meal may decrease systemic bioavailability and delay peak plasma concentrations. On the other hand, taking a meal activates proton pumps and stimulates acid secretion, but also buffers gastric acid. Both may increase the effect of medication in terms of maximum acid inhibition and its duration. The gastric acidity observed is a result of all of these factors.

The present study showed that during the 9-h daytime period, median gastric pH was increased by 0.9 and the percentage time for which gastric pH < 4 was more than halved when the drug was taken with breakfast. The inter-individual variation was considerable, which is consistent with many prior observations.

If the period of the breakfast meal and the next 45 min of the pH recording were omitted from analysis, in order to reduce the impact of the buffering effect of the meal, a numerical difference persisted, which was, however, not statistically significant. Buffering by food and the interaction between food and medication may therefore be an important explanation for improved acid control in this situation.

Patients who do not have breakfast could benefit from taking the drug in relation to lunch, which is usually a larger meal. Intake in relation to a meal may be even more important for the evening dose of a proton pump inhibitor, although this has not been studied. An evening dose of a drug is often taken inappropriately at bedtime, several hours after dinner; GERD patients should be advised to take their medication early in the evening before dinner. Taking a proton pump inhibitor in relation to dinner might sometimes be preferable to taking it in relation to breakfast, since a recent study showed that a dinnertime dose of omeprazole 40 mg controlled nocturnal gastric acidity significantly better than the same dose given in relation to breakfast.[15]

In summary, our study clearly shows an advantage in daytime intragastric pH control when omeprazole or lansoprazole is taken before breakfast compared with no breakfast. Therefore a morning dose of omeprazole or lansoprazole should be taken before a meal for optimal efficacy.

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