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Effects of a single dose of rabeprazole 20 mg and pantoprazole 40 mg on 24-h intragastric acidity and oesophageal acid exposure: a randomized study in gastro-oesophageal reflux disease patients with a history of nocturnal heartburn

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SUMMARY

Background
Nocturnal heartburn is common in patients with gastro-oesophageal reflux disease (GERD).

Aim
To compare the effects of single doses of rabeprazole 20 mg and pantoprazole 40 mg on 24-h intragastric acidity and oesophageal acid exposure (OAE).

Methods
A total of 52 subjects with GERD and a ≥6-month history of heartburn were randomized into a blinded, 2 × 2 crossover trial. Subjects' intragastric pH was monitored in two 48-h study periods with 6- to 13-day washout between periods. Patients received placebo on day 1, a single dose of rabeprazole 20 mg or pantoprazole 40 mg on day 2, and standardized meals throughout.

Results
The mean percentage time with intragastric pH >4 was significantly greater with rabeprazole vs. pantoprazole for the 24-h postdose interval (44.0% vs. 32.8%; $P < 0.001$). Significant differences were observed in the daytime (51.0% vs. 42.2%; $P < 0.001$) and nighttime (32.0% vs. 16.9%; $P < 0.001$). Rabeprazole was also significantly superior in other intragastric pH parameters. There was no statistical difference for OAE between treatments.

Conclusions
In GERD patients with nocturnal heartburn, rabeprazole 20 mg was significantly more effective than pantoprazole 40 mg in percentage time with intragastric pH >4 during the nighttime, daytime, and 24-h periods. Differences between treatments in OAE were not demonstrated. This trial is registered with clinicaltrials.gov, number NCT00237367.

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INTRODUCTION

Nocturnal heartburn symptoms are common in patients with gastro-oesophageal reflux disease (GERD).[1, 2] Farup and colleagues, in a US random-sample telephone survey, found a 14% prevalence of frequent GERD (≥1 symptom per week), with an overall prevalence of nocturnal GERD symptoms of 10%. Of patients with frequent GERD, 74% reported nocturnal symptoms.[1] These findings correlate with those of Shaker and colleagues, who reported that a Gallup survey of 1000 individuals with frequent heartburn (≥1 per week) found that 79% had nocturnal heartburn. Of these respondents, 75% reported that nocturnal symptoms affected their sleep.[2]

Sleep impairs oesophageal acid clearance, increasing acid contact time, and nocturnal acid reflux can increase the likelihood of oesophageal mucosal damage.[3] Nighttime heartburn, particularly when it interferes with sleep, significantly adds to the burden of illness of GERD, including reduced work productivity.[4] Compared with GERD patients who experience diurnal heartburn only, patients with nocturnal heartburn have significantly greater health-related quality-of-life impairment on the Medical Outcomes Study Short-Form 36 Health Survey ($P < 0.001$).[1]

Pantoprazole and rabeprazole are two proton pump inhibitors (PPIs) with the same mechanism of action, but with differences in their pharmacokinetic and pharmacodynamic properties.[5, 6] Pantoprazole has a longer half-life and a slower acid inhibition recovery rate compared with other PPIs. It has been suggested that this difference in duration of proton pump inhibition is related to its unique binding with cysteine 822, which is deeper in the membrane domain of the proton pump. This unique feature may indicate a longer duration of action for pantoprazole compared with the other PPIs.[6] Although clinical data are limited, these properties have been cited as evidence for the use of pantoprazole for control of nocturnal GERD symptoms.[3] With its higher pK_a, rabeprazole is less dependent on low pH for conversion to its active form. It is therefore rapidly activated over a wider pH range and has an early onset of acid inhibition.[7] An *in vitro* study of omeprazole, lansoprazole, pantoprazole and rabeprazole in hog gastric vesicles found that proton pump inhibition was >80% within 5 min of exposure to rabeprazole. In contrast, after 45 min, proton pump inhibition was <60% with pantoprazole.[8] Many authors have argued that it is the higher pK_a of rabeprazole that accounts for its faster onset of action and rapid inhibition of gastric acid secretion compared with omeprazole, lansoprazole and pantoprazole.[9–12] In a single-dose crossover study, Pantoflickova and colleagues investigated the effect on intragastric pH of omeprazole capsule 20 mg, omeprazole multiple-unit pellet system tablet 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and rabeprazole 20 mg in 18 healthy subjects (14- to 28-day washout period between treatments). Overall intragastric pH and time with pH >4 was significantly greater with single doses of rabeprazole compared with equal doses of omeprazole and higher doses of lansoprazole and pantoprazole ($P \leq 0.04$).[11]

Only one study compared rabeprazole and pantoprazole in their ability to control intragastric pH in patients with nocturnal GERD symptoms.[13] Relatively few studies have examined the effect of rabeprazole and pantoprazole on oesophageal acid exposure (OAE), with no comparative studies. The primary objectives of this trial were to compare the effects of a single dose of rabeprazole 20 mg with those of pantoprazole 40 mg on 24-h intragastric acidity and OAE in GERD patients with a history of nocturnal heartburn.

MATERIALS AND METHODS

Study design

This single-centre, investigator-blinded, 2×2 crossover trial randomized patients with GERD and a history of nocturnal heartburn to receive single doses of rabeprazole 20 mg and pantoprazole 40 mg. Patients participated in two 48-h study periods separated by a washout period of 6–13 days.

On day 1, subjects underwent oesophageal manometry prior to placement of the pH probe, to establish the location of the lower oesophageal sphincter (LOS) (unless LOS localization had previously been determined at the study site using this technique). Placement of the dual pH probe was accomplished via transnasal passage of a small flexible antimony probe assembly with two pH sensors spaced 15 cm apart for measurement of oesophageal and gastric pH (proximal sensor 5 cm above the LOS, distal sensor 10 cm below LOS).

Patients were given placebo on day 1 of each study period, followed by active treatment on day 2. The order of the study medication administration was randomly determined so that half the patients received

treatment with rabeprazole 20 mg then pantoprazole 40 mg, and half the patients received treatment with pantoprazole 40 mg then rabeprazole 20 mg. Both placebo and active treatments were given in the morning after an overnight fast.

Screening occurred within 28 days before patients received treatment. For each treatment period, at 7:00 AM, patients received an unmatched placebo tablet on day 1 and active treatment on day 2, with 8 oz of water. On both days, 60 min after dosing patients were given a standardized breakfast, and at approximately 1:00 PM, patients ate a standardized lunch. After a standardized dinner at approximately 6:00 PM, no further food or drink was permitted except for a 0.5-L bottle of water provided. Patients were domiciled for the 2-day treatment periods and remained under supervision throughout the day and overnight. Patients became recumbent at 10:00 PM and arose at approximately 6:00 AM the following morning. On day 3, patients were extubated. If data from any period could not be evaluated (e.g. pH monitor failure), the patient was asked to attend a repeat of the entire study period after a minimum 6-day washout.

Patients were randomized at the study site using medication numbers in permutated blocks and treatment-sequence assignments, with half the numbers assigned to each treatment sequence. The randomisation scheme was provided by Janssen Medical Affairs, LLC (currently Ortho-McNeil Janssen Scientific Affairs, LLC). Medication was distributed by a member of the study team in sequentially numbered, sealed envelopes, and patients were instructed to take the medication directly from the envelope to maintain blinding for study site personnel. During the study sessions, subjects remained under supervision throughout the day and overnight.

The study was conducted in accordance with the Declaration of Helsinki and its amendments, and the study protocol and amendments were reviewed and approved by the site's Institutional Review Board. Prior to study participation, written informed consent was obtained from each patient. This trial is registered with clinicaltrials.gov, number NCT00237367.

Patients

Male and female *Helicobacter pylori*-negative patients, assessed by finger stick test in the office, aged 18–65 years diagnosed with GERD accompanied by nocturnal heartburn were enrolled. Patients had a history of heartburn for ≥6 months, with an average of ≥3 episodes of heartburn per week (≥1 of which was nocturnal) in the month prior to screening and were required to have had OAE (defined as pH <4) ≥10% of the time documented by 24-h oesophageal pH monitoring performed at screening or within 24 months of screening. Women of child-bearing potential were required to have a negative pregnancy test at screening and day 1 of each treatment period and to be using an acceptable method of birth control.

Study exclusion criteria included diagnosis of a clinically significant gastrointestinal (GI) illness other than GERD; documented history of GI ulcer, GI haemorrhage, upper GI surgery, stricture, or oesophageal dilatation; chronic use of nonsteroidal anti-inflammatory drugs (including aspirin other than ≤81 mg) or cyclo-oxygenase 2 inhibitors and substance abuse or participation in a methadone treatment programme. Patients who were pregnant or breast-feeding or who had been diagnosed with cancer or were undergoing cancer treatment (with the exception of superficial skin malignancies) were also excluded.

Patients must not have participated in any investigational drug trial or used systemic corticosteroids, anticholinergics, antineoplastics, metoclopramide, anticoagulants, or tetracycline within 1 month of the screening visit. Patients must not have used histamine2-receptor antagonists (H2RAs), sucralfate, misoprostol, promotility agents, or any other drugs known to alter acid secretion or gastrointestinal motility within 14 days of randomisation. Any PPI was discontinued ≥10 days before randomisation or screening pH monitoring. During the study washout periods and in the period prior to randomisation when other GERD medications were prohibited, patients were allowed to use an antacid (TUMS, GlaxoSmithKline, London, UK) as rescue therapy. However, no antacids were permitted within 12 h before day 1 and during both treatment periods. Additionally, no alcoholic or caffeine beverages, grapefruit or grapefruit juice, smoking or exercise were permitted during both treatment periods.

Pharmacodynamic and safety assessments

For both treatment periods, intragastric and oesophageal pH were measured at 8-s intervals for 48 h using an indwelling, transnasal, dual pH probe assembly (Konigsberg Instruments, Inc., Pasadena, CA, USA) and data capture device (Digitrapper Synectics Mark III, Medtronics, Minneapolis, MN, USA) beginning

with administration of placebo on day 1. The pH scores provided in the Digitrapper device raw data files were corrected as indicated by the manufacturer's specifications.[14]

Safety and tolerability assessments were performed at screening during both treatment periods, and at the final visit. Samples for clinical laboratory testing, including haematology, biochemistry and urinalysis were taken at screening. A physical examination was performed and vital signs were obtained at screening and after completion of treatment period 2. All adverse events (AEs) experienced by patients, their severity and their relationship to study drug were recorded. Serious adverse events (SAEs) were defined as AEs that resulted in death or were life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, or were congenital abnormalities or birth defects.

Statistical analyses

The safety-evaluable population comprised all enrolled patients who received at least one dose of study drug. The per-protocol (PP) population, which was used to evaluate the primary endpoint, consisted of all patients who completed both treatment periods and took all doses of study medication, with ≥21 h of valid intragastric and oesophageal pH data, respectively, postdosing of active treatment for each study period. The intent-to-treat (ITT) population included those in the safety-evaluable population who had ≥1 post-baseline efficacy evaluation and ≥21 h of valid intragastric or oesophageal pH data. The ITT population was used to evaluate the primary endpoint as a confirmatory analysis. Data for 48-h ambulatory pH monitoring must have included ≥21 h with valid pH data postdosing of active treatment as assessed by the investigator.

Calculation of sample size was based on the null hypothesis that there would be no difference between treatments for percentage of time with intragastric pH >4 during a 24-h period and mean oesophageal reflux time over 24-h. To detect treatment difference, 48 evaluable patients would be required to achieve an 80% power at a 5% significance level. Assuming a 15% dropout rate, it was determined that 56 patients would need to be enrolled.

The primary pharmacodynamic endpoint was percentage of time with intragastric pH >4 during the 24-h period after a single dose of active treatment. Secondary intragastric pH endpoints included change from day 1 placebo baseline in percentage of time with pH >4 over 24 h, percentage of time with pH >3 over 24 h, mean 24-h pH, area under the curve (*AUC*) for 24-h pH, and 24-h integrated acidity. Oesophageal endpoints included percentage of time with pH <4 over 24 h (OAE), mean 24-h pH, *AUC* for 24-h pH, and 24-h integrated acidity. All of the above endpoints (with the exception of OAE) were also analysed for the daytime (7:00 AM to 10:00 PM) and nighttime (10:00 PM to 6:00 AM) intervals. Normalization of OAE during the daytime (pH <4 for <8% of the time period), nighttime (pH <4 for <3% of the time period) and 24-h periods (pH <4 for <4% of the time period), as defined by the site conducting the study, was also evaluated.

All statistical tests used to analyse the data were two-tailed and interpreted at the 5% significance level. For the primary efficacy variable, all continuous secondary efficacy endpoints and the change from baseline for pH measures, a linear mixed-effects analysis of variance (ANOVA) model was used to compare the difference between rabeprazole and pantoprazole. This model included fixed effects for sequence, period and treatment and a random effect for patients nested within sequence. A supplemental ANOVA model also included the additional fixed effect for percentage of time with intragastric pH >4 during the 24-h baseline period.

RESULTS

Patients

Fifty-two patients (28 female, 24 male; mean age 41 years) were randomized (safety-evaluable population), with 26 patients assigned to the treatment sequence rabeprazole/pantoprazole and 26 patients assigned to the pantoprazole/rabeprazole sequence. Mean baseline number of heartburn episodes per week was 5.9, of which 3.2 episodes were nocturnal (Table 1). No statistically significant differences in patient demographics (chi-square exact test; *t*-test) were observed between the rabeprazole/pantoprazole and pantoprazole/rabeprazole sequence groups (*P* values range from 0.114 to 0.842).

The safety population was composed of all 52 patients, and 50 patients completed the study (evaluable population for intragastric and oesophageal results). Two patients discontinued the study in period 2 of the rabeprazole/pantoprazole sequence due to

Table 1. Patient demographics

Characteristic	Treatment group sequences (ITT; n = 52)	
	Rabeprazole/ Pantoprazole (n = 26)	Pantoprazole/ Rabeprazole (n = 26)
Age, mean years ± s.d.	40.4 ± 12.91	41.1 ± 12.78
Gender, n (%)		
Male	11 (42.3)	13 (50.0)
Female	15 (57.7)	13 (50.0)
Ethnicity, n (%)		
Caucasian	23 (88.5)	23 (88.5)
Hispanic	1 (3.8)	0 (0.0)
Black	1 (3.8)	3 (11.5)
Asian	0 (0.0)	0 (0.0)
Other	1 (3.8)	0 (0.0)
BMI, mean kg/m^2 ± s.d.	32.6 ± 4.72*	30.4 ± 4.98
Duration of GERD symptoms, mean months ± s.d.	125.5 ± 88.70	147.7 ± 96.52
Heartburn episodes/ week in last month, mean n ± s.d.	6.0 ± 1.44	5.9 ± 1.61
Nocturnal heartburn episodes/week in last month, mean n ± s.d.	3.3 ± 2.09	3.1 ± 2.12

* n = 25.
BMI, body mass index; GERD, gastro-oesophageal reflux disease; ITT, intent-to-treat; s.d., standard deviation.

investigator-determined problems with pH evaluations and patient unwillingness/inability to repeat the test.

Primary pharmacodynamic analyses

Analyses of primary endpoints were conducted in both the PP (n = 50) and ITT (n = 52) populations. For mean percentage of time with intragastric pH >4 in the 24-h period after active treatment (Figure 1), rabeprazole 20 mg was found to be significantly more effective than pantoprazole 40 mg [PP population; rabeprazole, 44.0% (±18.72); pantoprazole, 32.8% (±16.94); $P < 0.001$]. Mean change from baseline in percentage of time with 24-h intragastric pH >4 for rabeprazole was also significantly greater compared with that for pantoprazole [PP population; rabeprazole, 30.3% (±18.68); pantoprazole, 19.2% (±17.22); $P < 0.001$]. For both these endpoints, similar and confirmatory results were found in the ITT population.

When comparing both treatments in individual subjects, more subjects had a greater degree of acid suppression after taking rabeprazole (39 subjects, 78.0%) than after taking pantoprazole (11 subjects, 22.0%) as measured by the primary endpoint ($P < 0.001$). In a *post hoc* analysis, the mean difference in percentage of time with intragastric pH >4 was 16.9% (±11.51) for rabeprazole-treated subjects who did better than pantoprazole-treated subjects and 9.4% (±10.02) for pantoprazole-treated subjects who did better than rabeprazole-treated subjects.

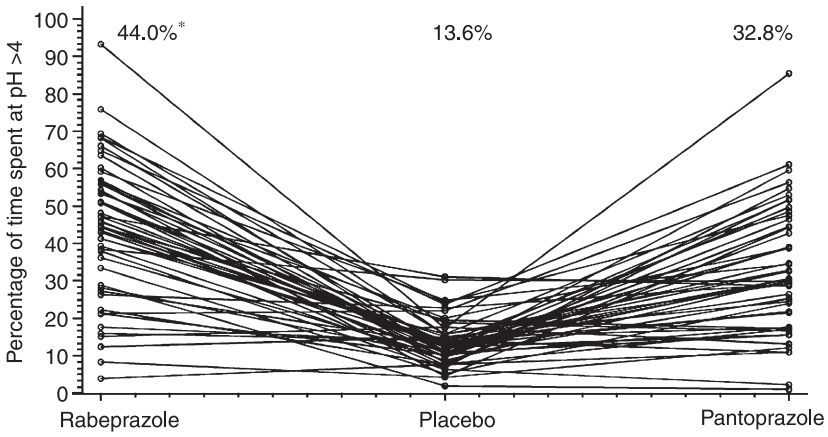

Figure 1. Percentage of time with intragastric pH >4 over 24 h by treatment group in the PP population.

*$P < 0.001$ compared with pantoprazole.
Data shown are for the per-protocol population (n = 50).
Percentages at top of figure represent the mean time with intragastric pH >4 in the 24-h period after active or placebo treatment.

Secondary pharmacodynamic analyses

Analyses of all secondary endpoints were conducted in the PP population. As with the 24-h period, mean percentage of time with intragastric pH >4 for the daytime (7:00 AM to 10:00 PM) and nighttime (10:00 PM to 6:00 AM) hours (Figure 2) was significantly greater with rabeprazole than with pantoprazole ($P < 0.001$ for both). This difference was particularly marked in the nighttime hours, with rabeprazole [32.0% (±26.39)], nearly double that with pantoprazole [16.9% (±19.91)] ($P < 0.001$). Time with intragastric pH >3 for the 24-h period postdose was significantly greater with rabeprazole than with pantoprazole: 56.1% (±20.94) vs. 45.5% (±18.06) ($P < 0.001$). Similarly, rabeprazole was more effective than pantoprazole in the daytime and nighttime intervals for this measure, again with the most marked difference seen in the nighttime period [rabeprazole, 44.1% (±29.54); pantoprazole, 26.6% (±25.27); $P < 0.001$].

Mean 24-h intragastric pH for rabeprazole was significantly higher compared with pantoprazole: 3.5 (±0.84) vs. 3.1 (±0.71) ($P < 0.001$). Mean daytime and nighttime intragastric pH also was significantly higher with rabeprazole vs. pantoprazole. Daytime pH with rabeprazole was 3.8 (±0.80) compared with 3.5 (±0.72) with pantoprazole ($P = 0.002$). Nighttime intragastric pH with rabeprazole was 3.1 (±1.17) vs. 2.4 (±0.91) with pantoprazole ($P < 0.001$). Compared with baseline placebo data, both study medications slowed the drop of intragastric pH after meals and kept nighttime pH higher. However, the median pH values on rabeprazole were greater than or equal to median pH values on pantoprazole at times beyond the first hour after dosing. The median pH on rabeprazole was noticeably higher than the median pH on pantoprazole at approximately hours 4–6, 7–11, 13–18, and 22–23. Median pH on rabeprazole also declined less rapidly after meal ingestion than did median pH on pantoprazole (Figure 3a,b).

Mean time with intragastric pH maintained above specific pH cutoffs was also analysed (Figure 4), with results showing that the number of hours spent above each pH cutoff value was significantly greater with rabeprazole vs. pantoprazole ($P \leq 0.002$).

Integrated acidity represents the cumulative time-weighted average of acid concentration and it has been suggested this measure may be more sensitive in detecting the change from baseline in gastric acidity attributable to an acid-mediating agent.[15] As with other measures, the treatment difference between rabeprazole and pantoprazole for integrated intragastric

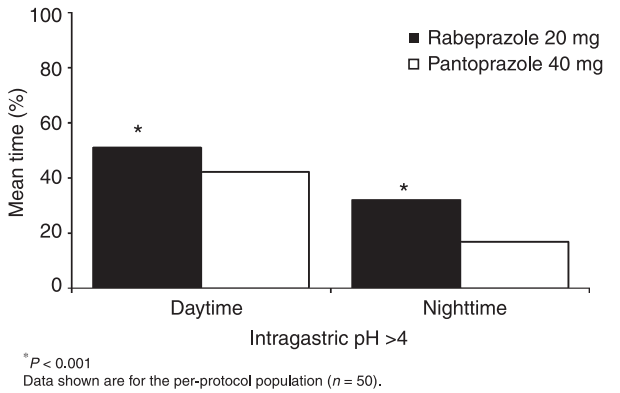

Figure 2. Mean time with intragastric pH >4 for the daytime and nighttime periods with rabeprazole 20 mg and pantoprazole 40 mg.

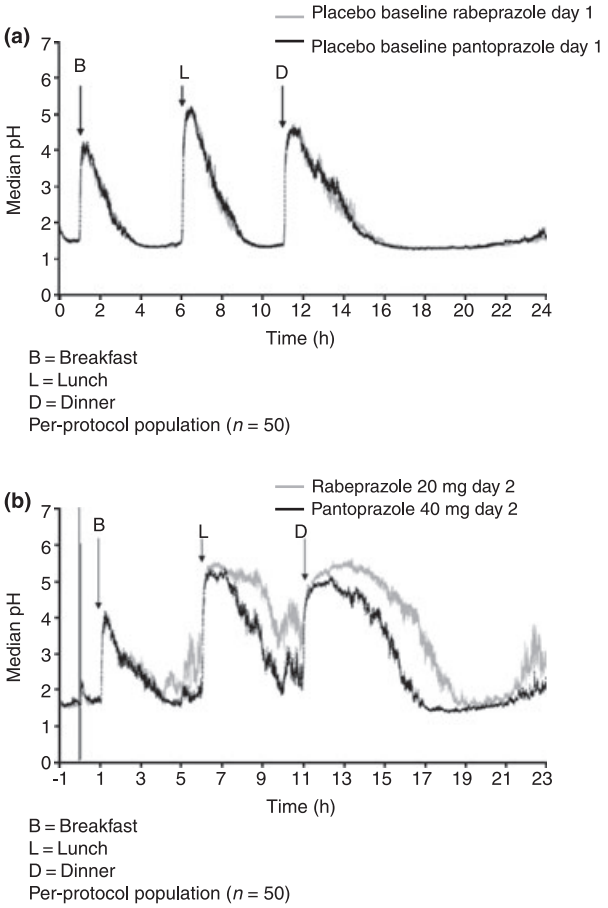

Figure 3. Median pH over 24 h (a) before (placebo baseline) and (b) after active treatment with rabeprazole 20 mg and pantoprazole 40 mg.

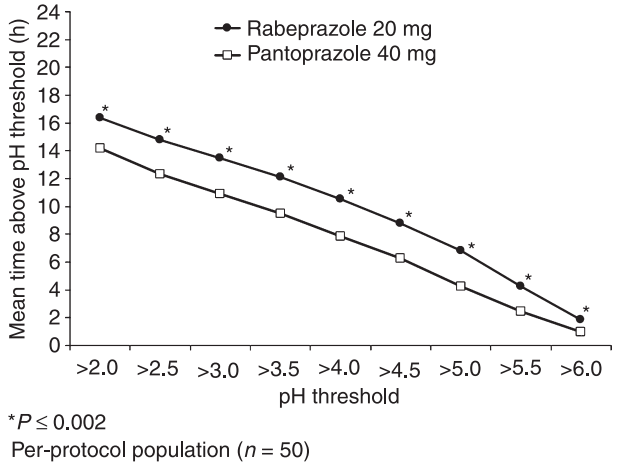

Figure 4. Mean time (in hours) with intragastric pH above selected thresholds over 24 h with rabeprazole 20 mg and pantoprazole 40 mg.

acidity was most apparent in the evening hours. For this measure, the difference in mean daytime intragastric acidity between rabeprazole and pantoprazole was not statistically significant; however, the difference was statistically significant in the nighttime hours [rabeprazole, 139.7 mmol·h/L (±116.00); pantoprazole, 200.6 mmol·h/L (±112.56); $P = 0.002$] and over the 24-h period [rabeprazole, 286.6 mmol·h/L (±217.05); 369.0 mmol·h/L (±187.80); $P = 0.006$]. For mean intragastric *AUC* for pH, rabeprazole was statistically significantly more effective than pantoprazole for all time intervals ($P \leq 0.002$). For the daytime (0-15 h postdose), nighttime (15-23 h postdose) and 24-h periods, results with rabeprazole were 57.0 pH units·h (±12.00), 24.5 pH units·h (±9.36) and 85.0 pH units·h (±20.06) respectively. For pantoprazole, the results were 52.0 pH units·h (±10.78), 19.3 pH units·h (±7.26) and 74.0 pH units·h (±17.07) for the daytime, nighttime and 24-h periods respectively.

Differences between the two agents were less pronounced for oesophageal pH parameters. Mean percentage of time with oesophageal pH <4 was similar for rabeprazole and pantoprazole: 5.8% (±4.79) compared with 5.8% (±4.45) (P = N.S.). Results for mean oesophageal pH, oesophageal *AUC*, nighttime oesophageal integrated acidity and 24-h OAE normalization measures also were similar for rabeprazole and pantoprazole. Results with rabeprazole were numerically but not statistically superior to pantoprazole for oesophageal integrated acidity for the daytime [rabeprazole, 2.8 mmol·h/L (±2.37); pantoprazole, 5.1 mmol·h/L (±15.47)] and 24-h [rabeprazole, 4.4 mmol·h/L (±4.31); pantoprazole, 7.8 mmol·h/L (±17.90)] periods and for the number of patients with OAE normalization for the daytime [rabeprazole, 36 (72.0%); pantoprazole, 32 (64.0%)] and nighttime [rabeprazole, 37 (74.0%); pantoprazole, 33 (66.0%)] periods. A numerical difference favouring rabeprazole was also observed in the mean change from baseline in percentage time that oesophageal pH <4 [rabeprazole −3.9% (placebo baseline 9.7); pantoprazole −3.6% (placebo baseline 9.4)].

Safety

No SAEs (either treatment related or otherwise) or deaths were reported during the study and no patient discontinued the study due to an AE. A total of 20 patients (38.5%) experienced ≥1 AE during the study, including before active-treatment dosing after enrolment. Seven patients experienced AEs considered possibly related to study medication (no AEs were considered probably or very likely related to study medication). Two patients (3.8%) experienced treatment-related AEs (diarrhoea and flatulence) after placebo dosing. Four patients (7.7%) and three patients (5.8%) respectively experienced treatment-related AEs after rabeprazole and pantoprazole treatment. These primarily consisted of GI disorders (rabeprazole: diarrhoea, flatulence, frequent bowel movements and vomiting; pantoprazole: upper abdominal pain, loose stools, nausea and vomiting). Most AEs were rated as mild, and no AE was experienced by >2 patients during each study period. The difference in incidence of AEs after rabeprazole vs. after pantoprazole was not clinically relevant. Study treatments had no effect on vital signs or physical examination results.

DISCUSSION

This study was designed to assess the pharmacodynamic effects of single doses of rabeprazole 20 mg and pantoprazole 40 mg in patients with nocturnal GERD symptoms, with an emphasis on comparisons during the nighttime hours. The unique binding properties of pantoprazole, resulting in a longer half-life and slower rate of recovery of acid inhibition, have been put forward as theoretical evidence supporting a longer duration of efficacy in gastric acid inhibition.[6] In the present study, for all intragastric pH parameters (including percentage of time with pH >4, change

from baseline in percentage of time with pH >4, mean pH, integrated acidity, and *AUC*), with the exception of daytime integrated acidity, results showed that rabeprazole was statistically significantly more effective than pantoprazole for each time interval studied. Differences between the two agents with respect to time with intragastric pH >3 and >4 were particularly marked during the nocturnal intervals, with percentage of time with intragastric pH >4 for rabeprazole (32.0%) nearly double that for pantoprazole (16.9%).

In other comparisons with pantoprazole in patients with GERD and in healthy volunteers, rabeprazole has been proved to be more effective in acid inhibition. In a study by Pantoflickova and colleagues comparing the acid inhibitory effects of single doses of rabeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and two formulations of 20-mg omeprazole in healthy volunteers, mean 24-h intragastric pH (3.4) and time with pH >4 (8 h) with rabeprazole was significantly greater than with all other agents ($P \leq 0.04$).[11] The results of a 5-way crossover trial investigating the day-5 effects on intragastric pH of esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with GERD by Miner and colleagues showed that rabeprazole resulted in a greater mean percentage of time with pH >4 (50.53%) and higher mean 24-h intragastric pH (3.7) vs. pantoprazole (41.94% and 3.3 respectively; no *P*-value comparison was reported).[16] The results for these measures in the present study were slightly lower for both agents – mean percentage of time with pH >4 over 24 h: 45.3% with rabeprazole vs. 32.9% with pantoprazole; mean 24-h intragastric pH: 3.5 with rabeprazole vs. 3.1 with pantoprazole. This may be because the present study is a single-dose study, while the Miner and colleagues study was a 5-day study that measured percentage of time at steady state.

Other studies of nocturnal intragastric acidity have compared the effects of rabeprazole with those of other PPIs. Luo and colleagues found that, in comparison with single doses of omeprazole 20 mg and pantoprazole 40 mg, a single dose of rabeprazole 10 mg significantly shortened the duration and raised the pH of nocturnal acid breakthrough (NAB) episodes (defined as gastric pH <4.0 for ≥1 h at night) ($P < 0.05$).[17] In a study by Warrington and colleagues, rabeprazole 20 mg resulted in a significantly longer time with intragastric pH >3 and >4 compared with esomeprazole 20 mg for the 0–14-, 14–24-, and 0–24-h postdose time intervals on day 1, and for the 14–24-h postdose time interval on day 5 ($P < 0.05$).[18]

There is considerable intra- and inter-individual variability in oesophageal reflux measures during 24- and 48-h ambulatory pH monitoring tests in patients with GERD.[19, 20] This recognized variability in oesophageal pH probably contributed to the difficulty in showing significant differences between rabeprazole and pantoprazole in reducing OAE. In addition, a relatively mild baseline level of OAE [9.69 (range 0.8, 26.4) in the rabeprazole group and 9.44 (range 1.8, 22.2) in the pantoprazole group] and normal OAE in a small number of subjects in either or both of the baseline periods may have mitigated the magnitude of observed treatment effect (supplementary Figure S1). Nevertheless, the similar reduction in OAE between rabeprazole and pantoprazole suggests that for patients with mild-to-moderate OAE, effective acid suppression with an agent of the PPI class, more so than relative potency within the class, may be the more important determinant of treatment response. Whether this also holds true for patients with more severe reflux is not addressed by our data and would require further study.

A possible limitation of this study is its experimental setting. Patients undergoing pH monitoring have been found to be more sedentary during testing than they would be on a typical day,[21, 22] which may affect their tendency to reflux. During the present study, patients remained under supervision for the testing period at the study site, ate standardized meals according to a prescribed regimen and were required to remain recumbent for a specified period. These circumstances are not those of a typical day (when patients are probably more active, experience more stress, etc.).

The single-dose design of this study is another limitation and prevents extrapolation of the results to a multiple-dose regimen. However, the results of the 5-day, 5-way crossover trial by Miner and colleagues suggest that the relative efficacy of rabeprazole compared with pantoprazole is not limited to a single dose.[16]

Lack of nocturnal gastric acid suppression, as well as a higher percentage of nocturnal OAE, has been associated with higher grades of GERD severity. Katz and colleagues noted that periods of reflux often occur during NAB and are seen more often in patients with more severe oesophageal mucosal damage (e.g. Barrett's oesophagus).[23] Similarly, Adachi and colleagues found that patients with higher grades of

erosive oesophagitis had a higher percentage of time with OAE during the nighttime hours compared with those with less severe erosive oesophagitis.[24] Although the present study did not investigate clinical endpoints, the pharmacodynamic effects of single doses of PPI may be relevant to the management of acid-related disease and thus have implications in clinical practice. For instance, the degree of acid suppression after the first dose may be important to a patient at the onset of continuous therapy. Alternatively, rapid and sustained-relief onset of action after a single dose may be relevant in patients who use PPIs intermittently or on-demand. The longer duration of gastric acid suppression during the nighttime hours observed with rabeprazole compared with pantoprazole in the present study may translate into a clinical benefit in terms of reduced nocturnal symptoms. Further study of the clinical implications of these findings is needed.

CONCLUSIONS

In GERD patients with nocturnal heartburn, a single dose of rabeprazole 20 mg was significantly more effective than pantoprazole 40 mg in mean percentage of time with intragastric pH >4 and in increasing mean time with intragastric pH >4 over baseline during the 24-h postdose period ($P < 0.001$ for both). Notably, time with intragastric pH >3 and >4 during the nighttime period, as well as the daytime and 24-h periods, was significantly greater with rabeprazole compared with pantoprazole (all $P \leq 0.018$). Differences between treatments in OAE were not demonstrated in this single-dose study. Both treatments were well-tolerated, with no difference in the incidence of AEs between agents.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Figure S1. Percentage of time spent at oesophageal pH <4 recorded postplacebo dosing on day 1 of each treatment period.

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