Comparative Efficacy of Rabeprazole and Pantoprazole in the Control of Nocturnal Acid Output and Intra-gastric Acidity

Hank S. Wang*, David S. Oh^{*,†}, Ariana Anderson[‡], Jose Nieto^{*,†}, Phuong Tien[†], Gordon Ohning^{*,†}, and Joseph R. Pisegna^{*,†}

**Department of Medicine, David Geffen School of Medicine at UCLA, [†]Department of Gastroenterology and Hepatology, Veterans Administration Greater Los Angeles Healthcare System and [‡]Department of Statistics, UCLA, Los Angeles, California, USA*

Background/Aims: Nocturnal reflux is a largely undiagnosed and unmanaged condition predisposing to multiple esophageal complications. We evaluated the effects of rabeprazole and pantoprazole on nocturnal intra-gastric pH and gastric acid output during Day 1 of therapy following the consumption of standard meals.

Methods: The study had a double-blinded, randomized, two-way crossover design, and involved 15 patients with a history of mild reflux. Following an overnight fast, patients were given either rabeprazole (20 mg) or pantoprazole (40 mg) prior to the first of three standard Western meals. They then underwent overnight continuous intra-gastric pH monitoring and gastric acid output measurement. The drug effect was analyzed using a two-treatment, two-period crossover mixed model. **Results:** The percentage of time during which the mean intra-gastric pH was greater than 4.0 and gastric acid output was less than 2.0 was higher for oral rabeprazole ($p < 0.05$). The inhibition of acid output was greater for rabeprazole at almost all time points. Furthermore, the mean time-matched pH values differed significantly over the first 8.3 hours ($p < 0.05$). **Conclusions:** On day 1, oral rabeprazole inhibited acid output to a greater extent and for a longer period than pantoprazole, and the intra-gastric pH was significantly higher for rabeprazole than for pantoprazole over the first 8.3 hours. (*Gut and Liver* 2008;2:30-38)

Key Words: Nocturnal; Reflux; Acid; Rabeprazole; Pantoprazole

INTRODUCTION

A recent Gallup survey conducted on behalf of the American Gastroenterological Association revealed the prevalence and severity of nocturnal heartburn in patients with gastroesophageal reflux disorder (GERD).¹ Overall, 79% of responders with at least weekly heartburn complained of nocturnal symptoms; moreover, the majority of these responders (70%) characterized their night-time discomfort as either moderate or severe.¹ Nocturnal GERD was disabling enough to affect sleep in 75% of responders, to negatively impact quality of sleep in 63% of responders and to impair ability to function the following day in 40% of responders.¹ Although cost analyses have not been published to date to determine the direct and indirect costs of managing undiagnosed and untreated nocturnal GERD they are likely to be high.²

Patients with GERD are particularly vulnerable to developing heartburn during night-time hours as a result of multiple mechanisms that increase esophageal acid exposure. Previously, it has been observed that increased acid output (AO) occurs in the late evening suggesting that a different, possibly more damaging, refluxate is present at night.³ In addition, diminished esophageal peristalsis may facilitate increased proximal reflux of gastric contents. Finally, protective mechanisms to maintain esophageal acid clearance are diminished at night including decreased saliva production, swallowing frequency and gastric emptying.⁴ When infused with acid, patients with GERD have been shown to have decreased acid clearance during sleep at night when compared to day-time hours.⁵

Correspondence to: Joseph R. Pisegna

David Geffen School of Medicine at UCLA, CURE: Digestive Diseases Research Center, Division of Gastroenterology and Hepatology, VA Greater Los Angeles Healthcare System, Building 115, Room 316, 11301 Wilshire Blvd, Los Angeles, CA. 90073, USA

Tel: 310-268-4069, Fax: 310-268-4096, E-mail: jpisegna@ucla.edu

Received on February 8, 2008. Accepted on April 15, 2008.

Prolonged exposure to the acidic gastric refluxate at night with the patient in the supine position has been directly associated with an increased risk of developing GERD complications, including erosive esophagitis, esophageal strictures and ulcerations, Barrett's esophagus and esophageal adenocarcinoma. Furthermore, during deep sleep, upper esophageal sphincter pressures have been shown to decrease dramatically to 8 ± 3 mmHg from 40 ± 17 mmHg when awake.⁶ Patients with unmanaged night-time reflux, therefore, are also at increased risk for multiple supra-esophageal complications including asthma, aspiration pneumonia as well as other laryngopharyngeal conditions.^{7,8}

Despite known prevalence and complications of unmanaged nocturnal GERD, few trials have evaluated drug therapies specifically targeting the night-time hours. A 2004 review by McGuigan *et al.* summarized 8 major trials evaluating efficacy of multiple proton pump inhibitors (PPIs) on night-time GERD symptoms, focusing only on subjective endpoints including frequency and severity of night-time heartburn and sleep disturbances.⁹ Other trials have measured objective endpoints, including 24-hour pH, but many have failed to specifically delineate nocturnal from diurnal results. No trials to date have evaluated the specific effect of different proton pump inhibitors on night-time pH and acid output. Furthermore, no study to date has evaluated rabeprazole as a potential therapeutic agent for night-time GERD.

In this study, we sought to compare rabeprazole and pantoprazole efficacy in the treatment of night-time GERD. Rabeprazole has been shown *in vitro* to be more readily converted to its active form than omeprazole, pantoprazole or lansoprazole.¹⁰ In addition, rabeprazole is known to have a faster onset of action in patients with heartburn leading some to suggest that rabeprazole may have efficacy as an on-demand or abortive therapeutic agent.¹¹ Given known pharmacokinetics regarding rabeprazole activation, we postulated that a single dose of rabeprazole, given prior to a standard Western meal, would yield greater acid output inhibition and a greater pH on the first day of assessment when compared to a single dose of pantoprazole. In addition, we sought to compare acid output with pH measurements to evaluate whether one measured outcome may be more relevant than the other in the evaluation of PPI efficacy.

MATERIALS AND METHODS

The study was conducted from 2004-2006 as a single-center, double-blinded, randomized two-way crossover study with baseline measurements enrolling 23 patients

with a history of GERD requiring antacids to control symptoms. The randomization scheme was computer generated and managed by a study pharmacist who provided treatment medications per protocol. Investigators remained blinded to treatment sequence until all patients had completed the study. All patients provided their informed consent to participate in the study. This study was approved by the Institutional Review Board of the VA Greater Los Angeles Healthcare System and conducted at the institution's General Clinical Research Center.

Men and women of any race, aged 18 to 65 years old, with a history of heartburn and symptoms with a frequency of at least 2 days per month over a 12 month period prior to screening were eligible for enrollment. Patients with a history of past or present endoscopic evidence of any significant esophageal pathology (ulcers, erosions) were excluded from study participation. Only patients with a negative *H. pylori* serology at study enrollment and no prior history of prior *H. pylori* eradication were included. Patients with a history of any of the following were excluded from the study: current pregnancy and/or a high likelihood of becoming pregnant during the study; gastric surgery; recent treatment with an histamine H₂-receptor antagonists, prostaglandin or sucralfate within 14 days prior to enrollment or with a proton pump inhibitor, prokinetic agent or bismuth subsalicylate within 30 days prior to enrollment; concurrent significant illnesses including cancer and renal or hepatic disease; any history of clinically significant alcohol abuse or other psychiatric illnesses; any predisposing condition that might interfere with the absorption, distribution, metabolism or excretion of any study drug; any history of multiple medication allergies or history of severe drug-associated adverse event. Subjects were not allowed to take corticosteroids, non-steroidal anti-inflammatory agents, H₂-receptor antagonists, non-study PPIs, sucralfate, prostaglandins, prokinetic agents, any anticholinergic drugs or bismuth subsalicylate during the study. In addition, patients were not allowed to smoke or consume any alcohol while on the study and were limited to 3 cups of caffeine-containing beverages per day.

Each patient arrived at the clinical research center for the baseline visit day at 0700 in a fasted state for at least 8 hours. Three meals, considered typical, standardized Western meals in terms of fat (108 gram), carbohydrate (319 gram) and protein (97 gram) composition were provided at 0800, 1200 and 1730. At 1700, a double lumen nasogastric (NG) tube with pH probe was passed into the stomach, and the tip of the pH probe was then positioned into the most dependent portion of the stomach.

Placement of the nasogastric (NG) tube was verified by auscultation of the epigastrium during air insufflation. Correct tube position was verified by water recovery of > 90% of injected 100 mL sterile water through the NG tube. Standard Western meal-stimulated gastric acid output was measured every 30 minutes (24 total observations) while intragastric pH was measured at every second (43,200 total observations) between 1900-0700. To calculate acid output, gastric fluid was aspirated continuously for 30 minutes to determine volume output (mL). The acid concentration of each 30-minute sample was determined using a Radiometer Copenhagen Titrator, with titration of the gastric sample to a pH of 7.0 using 0.1 N NaOH titrant. The 30 minute collection volume output was then multiplied by the acid concentration of that collection to calculate a 30 minute acid output. Hourly acid output was derived by extrapolating the 30 minute acid output value.

The subjects returned 1-2 weeks following the baseline visit for initiation of treatment period 1. Subjects were randomly assigned to one of two treatment groups. The subjects again fasted overnight and were given either rabeprazole 20 mg orally or pantoprazole 40 mg orally 30 to 45 minutes prior to breakfast. Each dose of study drug was placed in an opaque capsule and given to the patient by the research pharmacist and drug ingestion witnessed by the study coordinator. Patients then completed an identical protocol as described during the baseline visit. Following a washout period of 2-4 weeks, the subjects then returned for treatment period 2 whereby the study coordinator again witnessed medication administration.

The purpose of the study was to compare the efficacy of oral rabeprazole 20 mg against oral pantoprazole 40mg on nocturnal acid production on day 1 of therapy when given one hour prior to a standard Western meal. The study was designed as a double-blinded, randomized two-way crossover study whereby all enrolled patients underwent three total (baseline, treatment 1, treatment 2) nocturnal 12 hour measurements of gastric acid output and intragastric pH. Following screening laboratories and a full chart review, 23 patients were found to be eligible and were randomized into the study. Three patients were deemed unreliable and were excluded from the study following baseline assessment. Another 5 patients failed to complete both treatment periods due to discomfort caused by the NG tube. In total, 15 subjects completed the study. Due to mis-calibration, intragastric pH was inaccurately recorded over significant periods in 6 patients so that intragastric pH analysis was completed only in 9 study subjects. This number of study participants was considered adequate for statistical comparisons of the pri-

mary endpoints of the study. Baseline demographic and clinical characteristics are listed in Table 1. All enrolled patients complied with the study protocol and took all medications as witnessed by the study coordinator.

The primary endpoints of the study included gastric acid output and median pH over the 12 hour analysis, mean percentage of time with intragastric pH ≥ 4.0 and acid output ≤ 2.0 mEq/hr. All patients were encouraged to report adverse events both spontaneously and in response to general questioning. The study was terminated in patients who experienced adverse events, who developed significant intercurrent illnesses, and who exhibited unreliable behavior or who were suspected to have violated protocol.

Statistical comparisons of both acid output and pH were performed with analysis of variance and t-tests. If necessary, tests were preceded by a Shapiro-Wilk test to confirm normality of the data. The effect of each drug regimen on the 12-hr mean acid output was compared using a two-treatment, two-period (2 $\times$ 2) cross-over design model using SAS software. The mixed model included fixed effects for period, group, and treatment, and subject nested within group as a random effect. For all analyses, p-values <0.05 were considered significant. To evaluate treatment effects, confounding effects such as period and group effects were tested for significance and none were found to be significant.

pH-level sampling and tests were performed using R 2.1.1 for Windows. To obtain more observations and in-

Table 1. Baseline Clinical Characteristics (N=15)

Clinical characteristic	Number
Gender	
Male	11
Female	4
Age (years)	
Mean $\pm$ SD	54.5 $\pm$ 9.9
Range	31-67
Race	
Caucasian	6
African-American	6
Hispanic	3
Weight (kg)	
Mean $\pm$ SD	86.5 $\pm$ 16.4
Range	68.5-124.3
Height (cm)	
Mean $\pm$ SD	171.9 $\pm$ 9.1
Range	154.9-188.0
Body mass index (kg/m ²)	
Mean $\pm$ SD	29.3 $\pm$ 5.4
Range	24.1-42.9

crease statistical power, analysis of pH differences between treatments was preceded by sampling the paired differences leveled by patient and by time. Each difference series was constructed by subtracting the two time series for each patient under the two different treatments. A t-statistic was calculated for the aggregate sampled differences, and a hypothesis test was performed to test against the null hypothesis of the matched difference between treatments to be zero.

RESULTS

No serious adverse events or unscheduled terminations occurred due to medication intolerance. The most common complaints patients had while on the study protocol

Fig. 1. Mean percentage of time over the nocturnal hours on day 1 that intragastric pH is maintained greater than each specified threshold level by treatment group. Error bars ($\pm$ Standard Error) are shown for each curve. Note at pH > 6, overlap is seen between the rabeprazole and pantoprazole curves. Rabeprazole or pantoprazole is given 12 hours prior to measurement of intragastric pH.

included headache, nausea, bloating and diarrhea with an equal number of complaints attributed to both rabeprazole and pantoprazole. The mean number of evaluable hours from the baseline examination, rabeprazole treatment group and pantoprazole treatment group was 10 h 45 m, 10 h 30 m, and 10 h 45 m, respectively.

Oral rabeprazole sustained a significantly greater percentage of time during which mean pH was greater than 4.0 compared to oral pantoprazole (50.2% vs 16.0%). Overall, rabeprazole maintained mean pH at every threshold measured for a greater percentage of time as compared to pantoprazole (Fig. 1). A statistically significant difference was detected at every threshold measured between rabeprazole and pantoprazole except at pH > 6.0. Both pantoprazole and rabeprazole differed significantly from baseline at every level assessed. To display intragastric pH against time in a meaningful fashion, the median intragastric pH of every fourth second was plotted against time in Fig. 2. Here, rabeprazole produced a greater median intragastric pH roughly over the first half of observation, while pantoprazole appeared to maintain a greater median intragastric pH over the last half. Both study medications maintained an intragastric pH that was significantly greater than that recorded at the baseline visit.

The pH differences between treatments were further analyzed by sampling pseudo-random matched-pairs differences (Fig. 3). If the two treatments were equivalent in their effects on pH levels, the difference in pH at a specific time for a given patient should be approximately zero. A t-statistic was calculated to test this, and the null hypothesis of the mean matched-pairs difference being zero was not rejected ($p=0.30$). The mean difference in pH between pantoprazole and rabeprazole over the entire time-period was -0.3248 . The large p-value provides sufficiently strong evidence that the two treatments cannot be declared to have different effects in raising the pH of

Fig. 2. Nocturnal median intragastric 12-h pH monitoring profiles on day 1 of proton pump inhibitor therapy following administration of standard Western meals. Rabeprazole or pantoprazole is given 12 hours prior to measurement of intragastric pH.

Fig. 3. Nocturnal mean matched differences (pantoprazole-rabeprazole) over a 12-hour nocturnal period on day 1 of proton pump inhibitor therapy following administration of standard Western meals. A trend line imposed on the data indicates that rabeprazole maintains a significantly greater intragastric pH over the first 8.33 hours as compared to pantoprazole ($p < .04$). Rabeprazole or pantoprazole is given 12 hours prior to measurement of intragastric pH.

acid output when observed over the entire 12-hour period. However, a trend line imposed on the data suggests that the difference between pantoprazole and rabeprazole is negative for the first 30,000 observations (8.33 hours), indicating that treatment with rabeprazole is more effective in maintaining a higher pH over the first 8.33 hours. The hypothesis that the matched pH difference of pantoprazole-rabeprazole is negative is tested by sampling from only the first 30,000 observations of each difference series and was confirmed statistically significant ($p < 0.04$).

Using the same location of points as selected for the pantoprazole less rabeprazole differences over the entire time period, the difference in pH levels between the baseline and rabeprazole treatment is statistically significant, while the pH differences between pantoprazole and the baseline were not ($p > 0.10$). When Bonferroni adjustments for multiple comparisons were made, no pH differences were statistically significant. When using only the first 30,000 (8.33 hours) observations, all treatment differences between pantoprazole, rabeprazole and baseline are considered significant ($p < 0.05$). The rabeprazole-baseline comparison is most significant, with a p-value testing their difference to be less than 0.001.

Rabeprazole maintained mean acid output < 2.0 mEq/hr for a significantly greater mean percentage of time when compared to pantoprazole (91.9% vs 78.9%). Fig. 4 demonstrates that rabeprazole sustained mean acid output below every threshold assessed for a greater percentage of time when compared to treatment with pantoprazole. All threshold differences for pantoprazole and rabeprazole were statistically significant except for $AO < 0.5$. Percentage of time below threshold for both PPIs differed

Fig. 4. Mean percentage of time over the nocturnal hours on day 1 that gastric acid output is greater than each specified threshold level by treatment group. Rabeprazole or pantoprazole is given 12 hours prior to measurement of gastric acid output.

significantly from baseline at all levels ($p < 0.05$). Fig. 5 features a 12 hour acid output tracing plotted against time. Here, at nearly every time point observed, mean acid output measured on rabeprazole is less than that measured while on pantoprazole except for one occurrence noted at 0330. Although the mean acid output of rabeprazole was lower than the mean acid output of pantoprazole, the difference between the two treatment effects in the mixture model was not statistically significant ($p = 0.099$). The 95% confidence interval for the difference of least squares means, pantoprazole-rabeprazole, was $(-0.108, 1.100)$. Both study medications did significantly

Fig. 5. Nocturnal mean 12-h gastric acid output profiles on day 1 of proton pump inhibitor therapy following administration of standard Western meals. Rabeprazole or pantoprazole is given 12 hours prior to measurement of gastric acid output.

Fig. 6. Relationship between intragastric pH and gastric acid output measured at 30 minute intervals overnight for 9 individuals. Rabeprazole or pantoprazole is given 12 hours prior to pH and acid output measurement.

decrease measured acid output as compared to that measured at the baseline visit ($p < 0.05$).

In an attempt to compare acid output with intragastric pH to determine which may be a more meaningful clinical endpoint to assess PPI efficacy, we plotted AO against intragastric pH (Fig. 6). Given difficulties with calibration, comparison data between AO and intragastric pH was available only for 9 patients. In Fig. 6, acid output (mEq/hr) as measured at 30 minute intervals for all 9 patients under all three conditions (baseline, rabeprazole, pantoprazole) is plotted against mean intragastric pH calculated per 30 minutes. The regression line is plotted and a correlation coefficient of $r = -.56$ is calculated, indicating a moderately negative relationship between acid output and pH. For an increase in acid, there exists a reduction in pH levels. The conditional variance of the pH increases as acid output decreases, indicating that smaller levels of acid output have wider variations in the pH

levels. The correlation coefficient (r-squared) of .3163 indicates that 31.63% of the variation in pH levels can be explained by the acid output.

DISCUSSION

This study was conducted to evaluate the effectiveness of two FDA-approved proton pump inhibitors, pantoprazole and rabeprazole, to control gastric acidity during the nocturnal hours when a single oral dose was taken prior to breakfast in the morning. This is the first study to compare the effectiveness of PPIs to control gastric acid output and intragastric pH following a single oral dose of a PPI on day 1 of therapy when taken in the morning with a meal stimulus. The results indicate that both PPIs showed efficacy in reducing nocturnal gastric acid secretion. We determined that a single morning dose of oral rabeprazole 20 mg decreased acid output and maintained intragastric pH at least as effectively, if not more, than a single oral dose of pantoprazole 40 mg on day 1 of evaluation in patients with mild symptoms of reflux disease. Previous studies comparing rabeprazole with other PPIs have been limited and no study has evaluated acid output on proton pump inhibitor therapy during the night-time hours. In other comparative trials, rabeprazole has been shown to be a more potent acid inhibitor when compared to pantoprazole.¹¹⁻¹³ In 18 healthy controls, rabeprazole 20 mg once daily was superior to pantoprazole 40 mg once daily in maintaining percentage of time with $\text{pH} > 3$ and $\text{pH} > 4$ and in sustaining a pH of 3 for ≥ 3 h on day 1 of treatment.¹¹ Similarly, in patients with active peptic ulcer disease, rabeprazole 10 mg compared to pantoprazole 40 mg decreased incidence of nocturnal acid breakthrough (NAB), decreased persisting time of NAB and increased mean pH of NAB.¹² Finally, in a five-way crossover study comparing 5 different pro-

ton pump inhibitors, 34 patients with heartburn symptoms had intragastric pH measured following proton pump inhibitor treatment for 5 consecutive days. On day 5 assessment, rabeprazole maintained pH >4 for a greater percentage of time compared to pantoprazole and all other proton pump inhibitors evaluated except for esomeprazole.¹³

Several mechanisms may explain the superior efficacy of rabeprazole on increasing intragastric pH and decreasing acid output on the first day of therapy. Rates of acid inhibition are known to correlate with the acid stability of PPIs. Rabeprazole, which has the highest pKa of all PPIs and is therefore least stable at neutral pH, is more rapidly converted to inhibit the proton pump as compared to omeprazole, lansoprazole or pantoprazole.¹⁴ This may be critical given the known short half lives of PPIs that limit time available to accumulate in the parietal canaliculus, to form the activated sulphenamide form, and to bind to inactivate proton pumps.¹⁵ In addition, rabeprazole may have more prolonged and potent acid inhibitory effects due to continued binding to proton pump transmembrane domains even after achieving 100% inhibition of ATPase activity.¹⁰

While the majority of available parietal cells typically maintain an intracellular pH near 1, a proportion of these target cells may have a pH as high as 3 depending largely on the age of that cell.¹¹ In extremely acidic environments, proton pump inhibitors may have similar equipotency.¹¹ However, in less acidic environments, rabeprazole, given its rapid activation over a wide pH range, actually targets a greater population of parietal cells to give a more rapid and pronounced degree of acid inhibition.¹⁶ In older parietal cells, rabeprazole can be as much as 10 times more potent than other proton pump inhibitors.¹¹ In addition, rabeprazole has an advantage not shared by other proton pump inhibitors. Its metabolism is largely nonenzymatic and therefore less dependent on CYP2C19, giving a greater consistency of pharmacokinetics across all patients, regardless of CYP2C19 genotype.¹⁷

In this study, a single dose of rabeprazole given before a standard Western meal inhibited acid output to a greater degree and over a longer period of time compared to a single dose of pantoprazole. Food and nutrients are a natural physiological stimulant for acid secretion, and by controlling each subject's diet and ensuring that all were fed a standard Western meal, we were able to reliably evaluate PPI efficacy in a realistic model. Previously, it has been shown that acid output in normal subjects peaks approximately 1.5 hours after a meal and gradually decreases over the next 2.5 hours so that at 4 hours post meal, acid output remains at 1/4 peak AO production.¹⁸

In the current study, rabeprazole suppressed acid output to a greater degree than pantoprazole over the entire observation period, including the post-meal hours (Fig. 5). One distinct difference noted at 03:30 (8.5 hours into the study), when mean acid output is minimally greater under rabeprazole, most likely represents an anomalous value as subsequent measurements then demonstrate decreased acid output under rabeprazole.

Oral rabeprazole also maintained an overall greater median pH on day 1 of dosing over the nocturnal hours as compared to pantoprazole (Fig. 2). When pH differences were further evaluated by sampling matched differences (pantoprazole-rabeprazole), no significant difference between the two treatments were detected over the entire 12 hour period. The trend line in Figure 3, however, suggests a persistent difference between mean differences in pH over the first 8.33 hours that was confirmed to be statistically significant ($p < .04$). Therefore, over the first 8.33 hours, rabeprazole maintains a pH that is greater than that of pantoprazole when matched by patient and time.

No study to date has evaluated the utility of measuring acid output versus intragastric pH to assess proton pump inhibitor efficacy. The difficulties in measuring and interpreting intragastric pH have been well documented previously.^{19,20} For instance, Fisher et al. demonstrated regional differences in gastric acidity in the four quartiles of the stomach in response to food stimulation, suggesting that a single pH electrode may not adequately reflect gastric pH.²¹ Furthermore, quantitative measurements of intragastric pH using an electrode and aspiration of gastric juice have produced significantly different results. In contrast, acid output measurement may be a superior method to documenting effective PPI therapy because it takes into account the complete gastric aspirate rather than depend on an isolated intragastric measurement. Furthermore, newer techniques in measuring acid output employing direct visualization of gastric contents during endoscopy may lead to enhanced accuracy and reproducibility.²²

In this study, a poor correlation was noted between gastric acid output and intragastric pH, consistent with previously published data.²³ Acid output ranged from .17-3.50 mEq/hr while intragastric pH ranged from 1.00-3.81 (Fig. 6). Intragastric pH was not an accurate predictor of AO and vice versa. For instance, at an extremely low acid output (<.5 mEq/hr), a wide variability of intragastric pH (1.5-3.5) is observed at levels lower than expected. Similarly, patients with the lowest levels of pH detected did not have the highest levels of acid output measured. Overall, pH did not appear to correlate well with acid output in this study. Given its lack of de-

pendence on volume present in the stomach, intragastric pH is likely to be a less reliable measure of PPI efficacy as compared to acid output.

Given known prevalence and complications of unmanaged nocturnal GERD, we sought to evaluate, for the first time, the effect of rabeprazole on nocturnal acid output and intragastric pH. In this study, on day one of dosing with a PPI given 30 minutes before a standard Western meal, rabeprazole inhibited acid output to a greater extent and for a greater period as compared to pantoprazole during the night-time hours from 1900 to 0700. Rabeprazole was able to maintain a significantly greater median intragastric pH over the first 8.33 hours of the nocturnal period. Acid output may be a more relevant clinical outcome to assess PPI therapy because it depends on both acid concentration and volume whereas intragastric pH is measured from a random gastric sample that may not reflect the true acidity of the stomach's contents. Further studies in assessing PPI efficacy should assess intragastric pH, acid output, and employ a validated questionnaire to evaluate symptomatic improvement of nocturnal complaints. To further elucidate rabeprazole's role as an abortive therapeutic agent, further studies measuring its effect on acid output and intragastric pH immediately following dosage should be performed.

ACKNOWLEDGEMENTS

This study was funded in part by Eisai Inc. and Pri-Cara, Unit of Ortho-McNeil, Inc. The study sponsor played no role in the collection, analysis and interpretation of the data.

REFERENCES

- Shaker R, Castell DO, Schoenfeld PS, Spechler SJ. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. *Am J Gastroenterol* 2003; 98:1487-1493.
- Mason J, Hungin AP. Review article: gastro-oesophageal reflux disease--the health economic implications. *Aliment Pharmacol Ther* 2005;22:S20-31.
- Moore JG, Halberg F. Circadian rhythm of gastric acid secretion in men with active duodenal ulcer. *Dig Dis Sci* 1986;31:1185-1191.
- Castell DO, Murray JA, Tutuian R, Orlando RC, Arnold R. Review article: the pathophysiology of gastro-oesophageal reflux disease-oesophageal manifestations. *Aliment Pharmacol Ther* 2004;20:S14-25.
- Orr WC, Robinson MG, Johnson LF. Acid clearance during sleep in the pathogenesis of reflux esophagitis. *Dig Dis Sci* 1981;26:423-427.
- Kahrilas PJ, Dodds WJ, Dent J, et al. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. *Gastroenterology* 1987;92:466-471.
- Pisegna J, Holtmann G, Howden CW, et al. Review article: oesophageal complications and consequences of persistent gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2004;20:S47-56.
- Fass R, Achem SR, Harding S, Mittal RK, Quigley E. Review article: supra-oesophageal manifestations of gastro-oesophageal reflux disease and the role of night-time gastro-oesophageal reflux. *Aliment Pharmacol Ther* 2004; 20:S26-38.
- McGuigan JE, Belafsky PC, Fromer L, et al. Review article: diagnosis and management of night-time reflux. *Aliment Pharmacol Ther* 2004;20:S57-72.
- Besancon M, Simon A, Sachs G, Shin JM. Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. *J Biol Chem* 1997;272:22438-22446.
- Pantoflickova D, Dorta G, Ravic M, Jornod P, Blum AL. Acid inhibition on the first day of dosing: comparison of four proton pump inhibitors. *Aliment Pharmacol Ther* 2003;17:1507-1514.
- Luo JY, Niu CY, Wang XQ, Zhu YL, Gong J. Effect of a single oral dose of rabeprazole on nocturnal acid breakthrough and nocturnal alkaline amplitude. *World J Gastroenterol* 2003;9:2583-2586.
- Miner P Jr, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol* 2003;98:2616-2620.
- Ohning GV, Walsh JH, Pisegna JR, et al. Rabeprazole is superior to omeprazole for the inhibition of peptone meal-stimulated gastric acid secretion in *Helicobacter pylori*-negative subjects. *Aliment Pharmacol Ther* 2003;17: 1109-1114.
- Williams MP, Sercombe J, Hamilton MI, Pounder RE. A placebo-controlled trial to assess the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. *Aliment Pharmacol Ther* 1998;12: 1079-1089.
- Robinson M. Review article: pH, healing and symptom relief with rabeprazole treatment in acid-related disorders. *Aliment Pharmacol Ther* 2004;20:S30-37.
- Horn J. Review article: relationship between the metabolism and efficacy of proton pump inhibitors--focus on rabeprazole. *Aliment Pharmacol Ther* 2004;20:S11-19.
- Fordtran JS, Walsh JH. Gastric acid secretion rate and buffer content of the stomach after eating. Results in normal subjects and in patients with duodenal ulcer. *J Clin Invest* 1973;52:645-657.
- Johnston DA, Wormsley KG. Problems with the interpretation of gastric pH measurement. *Clin Invest* 1993; 72:12-17.
- Fisher RS, Sher DJ, Donahue D, Senior J, Krevsky B. A single intragastric pH electrode does not accurately measure intragastric acidity. *Am J Gastroenterol* 1996;91:1167-1172.
- Fisher RS, Sher DJ, Donahue D, et al. Regional differences

- in gastric acidity and antacid distribution: is a single pH electrode sufficient? *Am J Gastroenterol* 1997;92:263-270.
22. Oh DS, Wang HS, Ohning GV, Pisegna JR. Validation of a new endoscopic technique to assess acid output in Zollinger-Ellison syndrome. *Clin Gastroenterol Hepatol* 2006;4: 1467-1473.
23. Pratha VS, Hogan DL, Lane JR, et al. Inhibition of pentagastrin-stimulated gastric acid secretion by pantoprazole and omeprazole in healthy adults. *Dig Dis Sci* 2006;51: 123-131.