Ther Adv Gastroenterol
2015, Vol. 8(6) 322–330
DOI: 10.1177/1756283X15592583

Daytime intragastric acid control: *post hoc* analyses of esomeprazole 20 mg and over-the-counter proton-pump inhibitors

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Abstract

Objectives: In mild gastroesophageal reflux disease, which accounts for the great majority of cases, the major burden of reflux occurs during daytime hours, after food intake. The aim of these analyses was to evaluate intragastric pH control during the typical 14-hour daytime awake period by proton-pump inhibitors (PPIs) given at over-the-counter (OTC) dosages.

Methods: In one double-blind and three open-label, randomized, crossover studies, intragastric pH was monitored for 24 hours on day 5 of treatment. The 24-hour data have been reported previously. *Post hoc* analyses reassessed these studies for the 14-hour daytime period, comparing esomeprazole 20 mg with currently available OTC PPIs omeprazole, pantoprazole (not available in the US) and lansoprazole.

Results: Subjects maintained intragastric pH >4 for a significantly greater mean percentage of the 14-hour daytime period with esomeprazole 20 mg compared with any of the PPI comparators at OTC dosages. Geometric mean ratios (95% confidence intervals) for esomeprazole 20 mg *versus* the comparators were: 1.45 (1.14–1.85; $p = 0.003$) *versus* omeprazole 20 mg; 2.50 (2.01–3.11; $p < 0.0001$) *versus* pantoprazole 20 mg; and 1.69 (1.46–1.97; $p < 0.0001$) and 1.89 (1.05–3.37; $p = 0.03$) *versus* lansoprazole 15 mg. A greater proportion of subjects had better pH control with esomeprazole than with the other PPIs (range: 69–97%).

Conclusions: Across the 14-hour daytime period, esomeprazole 20 mg once daily given 30 minutes before breakfast for 5 days provided acid control for a significantly greater average proportion of time *versus* the PPI comparators omeprazole, pantoprazole and lansoprazole at currently available OTC dosages.

Keywords: esomeprazole, gastric acid inhibitors, gastroesophageal reflux, intragastric pH, proton pump inhibitors

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Introduction

Esophageal pH monitoring studies lasting 24 hours in patients with gastroesophageal reflux disease (GERD) have distinguished two main patterns of the timing of acid reflux occurrence [Adachi *et al.* 2001; Gudmundsson *et al.* 1988; Masclee *et al.* 1990]. Individuals with more severe underlying disease, based on the presence of severe esophagitis (Los Angeles grades C or D), have consistently high levels of acid exposure across the entire 24-hour period [Adachi *et al.* 2001; Masclee *et al.* 1990]. In contrast, the most common pattern of 24-hour esophageal acid exposure is seen in patients with milder GERD (Los Angeles grades A or B erosive esophagitis, or nonerosive disease), in whom the majority of acid reflux episodes occur during daytime waking hours [Adachi *et al.* 2001; Gudmundsson *et al.* 1988; Masclee *et al.* 1990] and are driven by food intake-stimulated acid secretion [Dent, 1994] and an increased risk for occurrence of acid reflux during transient lower esophageal sphincter relaxations [Dent *et al.* 2013].

Studies of acid exposure in patients with milder GERD demonstrate that acid exposure varies substantially through the day, increasing sharply in the 3 hours after each meal and with the greatest increase occurring after the evening meal [Gudmundsson *et al.* 1988; Johnsson *et al.* 1992]. Episodes of heartburn and regurgitation generally follow this pattern of acid reflux [Dent *et al.* 2012; Johnsson *et al.* 1992], but nighttime symptoms [Shaker *et al.* 2003] and sleep dysfunction associated with GERD [Kulig *et al.* 2003] remain problematic across the whole spectrum of GERD patients (i.e. including esophagitis grade A and B and nonerosive disease). As such, therapy for patients who have milder forms of GERD [Dent *et al.* 2012] and experience both nighttime and daytime symptoms should focus primarily on controlling acid secretion during awake hours, consistent with the observed pattern of acid episodes.

Given the importance of reflux during the daytime awake period in mild GERD, the objective of these *post hoc* analyses was to evaluate intragastric pH during the daytime awake period only. The effects of esomeprazole 20 mg and other proton-pump inhibitors (PPIs) at currently approved over-the-counter (OTC) doses on intragastric pH during the 14-hour daytime awake period were explored using data from 4 previously published studies [Lind *et al.* 2000; Röhss *et al.* 2004; Wilder-Smith *et al.* 2007, 2008]. A 14-hour period was chosen as representative of the typical 'awake' period because that interval would capture the main times during which food normally stimulates acid secretion, resulting in the greatest amount of acid reflux and potential for symptoms.

Methods

Study design

We re-analyzed the four completed randomized, crossover studies that evaluated intragastric pH in healthy subjects or patients with GERD who received treatment with esomeprazole 20 mg compared with what is now an approved OTC dosage of another PPI [Lind *et al.* 2000; Röhss *et al.* 2004; Wilder-Smith *et al.* 2007, 2008]. Because evaluation of intragastric pH during the 0–14 hour period was not included in the original analyses, these new analyses could be performed only in studies from which raw data were available. Four published studies comparing esomeprazole 20 mg with another PPI have not been included in these analyses: two studies were excluded because the comparator PPI, rabeprazole, is not approved as an OTC medication [Röhss *et al.* 2004; Warrington *et al.* 2002]; one study with omeprazole [Miehlke *et al.* 2011] and one with pantoprazole [Röhss *et al.* 2004] were excluded because relevant raw data were not available. All studies were conducted according to the ethical principles of the Declaration of Helsinki, and the protocols were approved by relevant independent ethics committees at study sites. All subjects provided written, informed consent.

Study population

Two of the included trials were conducted in healthy volunteers [Röhss *et al.* 2004; Wilder-Smith *et al.* 2007] and two in patients with GERD [Lind *et al.* 2000; Wilder-Smith *et al.* 2008]. Subjects were males and females aged 20–60 years without significant concomitant diseases. The majority were *Helicobacter pylori* negative, with the exception of six *H. pylori* positive subjects in the study by Lind and colleagues [Lind *et al.* 2000].

Study drugs and administration

All subjects received esomeprazole 20 mg (administered as 22.3 mg esomeprazole magnesium trihydrate) and one of three comparator PPIs administered at approved OTC dosages, i.e. omeprazole 20 mg [Lind *et al.* 2000], pantoprazole 20 mg (administered as 22.6 mg pantoprazole sodium sesquihydrate) [Röhss *et al.* 2004; Wilder-Smith *et al.* 2008], or lansoprazole 15 mg [Röhss *et al.* 2004; Wilder-Smith *et al.* 2007]. Some of these studies also included additional treatment arms with higher doses of esomeprazole and the comparator PPIs as part of the crossover design (Table 1). Analyses of these doses were not included here since they are less relevant to mild GERD. All drugs were administered once daily in the morning 30 minutes before breakfast during treatment periods of 5 days separated by washout periods of at least 13–14 days. The sequence for the treatment periods was randomly allocated. Treatment assignment was double-blinded in one study [Lind *et al.* 2000] and open label in the remaining three studies [Röhss *et al.* 2004; Wilder-Smith *et al.* 2007, 2008].

Study measurements

Detailed descriptions of the study procedures were included in the previously published individual studies [Lind *et al.* 2000; Röhss *et al.* 2004; Wilder-Smith *et al.* 2007, 2008]. Briefly, intragastric pH

Table 1. Characteristics of intragastric pH studies included in analyses.

Study	Design	Study population	*n**	Percent male (%)	Mean age (years)	Treatment intervention[$]
Lind *et al.* [2000]	Double-blind, randomized crossover study	GERD symptoms or diagnosis Male and female Aged 30–60 years	36	42	45	Esomeprazole 20 mg *Esomeprazole 40 mg* Omeprazole 20 mg
Wilder-Smith *et al.* [2008]	Open-label, randomized crossover study	GERD symptoms[‡] Male and female Aged 20–60 years	38	56	30.4	Esomeprazole 20 mg *Esomeprazole 40 mg* *Esomeprazole 80 mg* Pantoprazole 20 mg[§] *Pantoprazole 40 mg* *Pantoprazole 80 mg*
Wilder-Smith *et al.* [2007]	Open-label, randomized single-center, crossover study	Healthy volunteers Male and female Aged 20–60 years	37	46	30.9	Esomeprazole 20 mg *Esomeprazole 40 mg* *Esomeprazole 80 mg* Lansoprazole 15 mg *Lansoprazole 30 mg* *Lansoprazole 60 mg*
Röhss *et al.* [2004]	Open-label, randomized crossover study	Healthy volunteers Male and female Aged 20–50 years	26	63	26.2	Esomeprazole 20 mg Lansoprazole 15 mg

*Number of subjects with data on one or both treatments of interest in the current *post hoc* analyses.
[$]Treatment arms for each study. Doses shown in italics were not included in the current *post hoc* analyses.
[‡]Mild-to-moderate heartburn and/or acid regurgitation on ⩾2 days/week for ⩾2 months prior to the study.
[§]Pantoprazole 20 mg is available as an OTC medication in various countries outside the US (e.g. countries in the European Union, Argentina, Mexico, Australia, and New Zealand).
GERD, gastroesophageal reflux disease; OTC, over-the-counter.

was monitored for 24 hours on day 5 of each treatment period after an overnight fast. Following study drug administration, continuous 24-hour intragastric pH was measured using a microelectrode positioned about 10 cm below the lower esophageal sphincter. Subjects remained at the study centers during pH monitoring and received standardized meals to ensure consistency of results.

Outcome assessments

Results of the *a priori* analyses of intragastric acid control across the full 24-hour period have been previously reported [Lind *et al.* 2000; Röhss *et al.* 2004; Wilder-Smith *et al.* 2007, 2008]. For the purposes of the current analyses, intragastric acid control was reassessed for the 14-hour daytime period, defined as 0–14 hours post dose. The primary objective of these analyses was to evaluate the percentage of time with intragastric pH >4 during the 14-hour daytime period after 5 days of PPI use. Secondary objectives were to: evaluate the proportion of subjects with a 'better' response with esomeprazole *versus* the PPI comparator (determined by the duration of time with pH >4 in the 14-hour daytime awake period); assess the mean gain in time with pH >4 for those with a better response with esomeprazole *versus* the PPI comparator; and compare the degree of intersubject variability of pH control for each treatment period for each dosing comparison.

Statistical analyses

The mean percentage of the 14-hour daytime period, and 95% confidence interval (CI), with pH >4 was estimated for each study using a linear mixed-effect model that included factors for treatment, treatment period and treatment sequence as fixed effects, and a factor of subject nested with treatment sequence as a random effect. Using the same model, geometric mean ratios and 95% CIs were estimated based on log-transformed individual values. The proportion of subjects with a better response to esomeprazole *versus* the PPI comparator was calculated based on the time with pH >4 in the 14-hour daytime period for one *versus* the other. For each dose comparison, the null hypothesis that the proportion was 0.5 was analyzed using a binomial test. The mean increment of time with pH >4 for those with a better response to esomeprazole *versus* the PPI comparator was calculated for each study based on the difference between the treatment periods in total time with pH >4 across the 14-hour daytime period. For the purpose of illustrating the interindividual variability of response of intragastric pH and rate of incomplete response with esomeprazole *versus* the PPI comparators, median intragastric pH profiles with 25th percentiles were calculated for each comparison based on individual 1-hour intragastric pH values over the 14-hour analysis period.

Results

The data of 137 subjects in the four studies were analyzed. The characteristics of the subjects included in these studies and the PPIs taken are summarized in Table 1.

The primary outcome of these analyses was the proportion of time during the 14-hour daytime period that the intragastric pH remained >4 for esomeprazole 20 mg and comparator PPIs; results are shown in Figure 1 and Table 2. Subjects maintained intragastric pH >4 for a significantly higher mean percentage of the 14-hour daytime period with esomeprazole 20 mg compared with any of the PPI comparators at OTC dosages. The geometric mean ratios (95% CI) for esomeprazole 20 mg *versus* the comparators ranged from 1.45 (95% CI 1.14–1.85; $p < 0.01$ *versus* omeprazole 20 mg) to 2.50 (95% CI 2.01–3.11; $p < 0.0001$ *versus* pantoprazole 20 mg), indicating that the benefit for esomeprazole 20 mg was roughly 1.5–2.5 times that of the other PPIs evaluated (Table 2).

Figure 2 shows the median (and 25th percentile) intragastric pH on day 5 of dosing during the 14-hour daytime awake period for the comparisons of esomeprazole 20 mg with omeprazole 20 mg (Figure 2a), pantoprazole 20 mg (Figure 2b) and lansoprazole 15 mg (Figure 2c and Figure 2d). These plots show that the hourly 25th percentile pH values with esomeprazole were nearly always higher than the comparable 50th percentile values for the comparators.

Analyses of individual patient responses showed that a better response (more time with intragastric pH >4 in the 14-hour daytime period) was achieved in a higher percentage of subjects in the treatment periods with esomeprazole 20 mg relative to omeprazole 20 mg (75% *versus* 25%; $p = 0.0027$), pantoprazole 20 mg (97% *versus* 3%; $p < 0.0001$) and lansoprazole 15 mg (86% *versus* 14%, $p < 0.0001$ in study 3; 69% *versus* 31%, $p = 0.0499$ in study 4) (Table 3). Overall across the 4 studies, 82.7% of

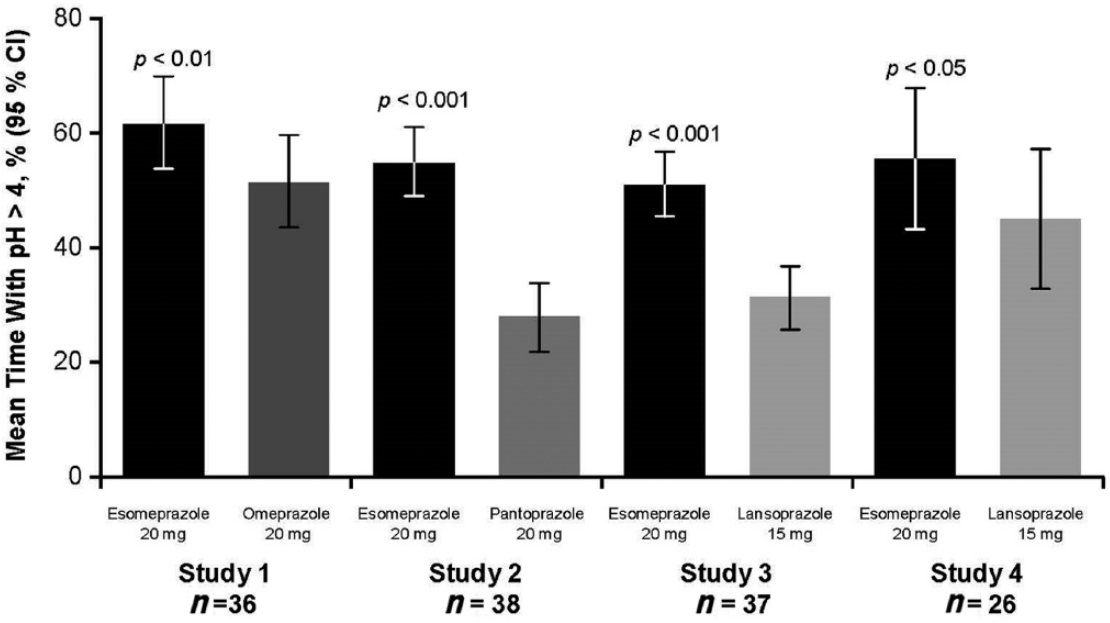

Figure 1. Mean percentage (95% CI) of the 14-hour daytime period with intragastric pH >4 for esomeprazole 20 mg *versus* over-the-counter proton-pump inhibitors.
CI, confidence interval.

Table 2. Percentage of time with pH >4 during the 14-hour daytime period and geometric mean ratios.

Study	*n**	Treatment intervention$	Mean percentage of time (95% CI) with pH >4 (%)	Geometric mean ratio (95% CI), esomeprazole 20 mg/comparator
1	36	Esomeprazole 20 mg	61.9 (53.9–69.9)‡	1.45 (1.14–1.85)‡
		Omeprazole 20 mg	51.7 (43.7–59.7)	
2	38	Esomeprazole 20 mg	55.2 (49.2–61.1)§	2.50 (2.01–3.11)§
		Pantoprazole 20 mg	28.0 (22.0–34.0)	
3	37	Esomeprazole 20 mg	51.2 (45.6–56.8)§	1.69 (1.46–1.97)§
		Lansoprazole 15 mg	31.5 (25.9–37.0)	
4	26	Esomeprazole 20 mg	55.8 (43.5–68.0)‖	1.89 (1.05–3.37)‖
		Lansoprazole 15 mg	45.2 (33.0–57.5)	

*Number of subjects with data on one or both treatments of interest in the current *post hoc* analyses.
$Treatment arms evaluated in current *post hoc* analyses.
‡$p < 0.01$
§$p < 0.0001$ *versus* comparator
‖$p < 0.05$
CI, confidence interval.

patients had a better response when receiving esomeprazole. The mean increment of time during which intragastric pH was >4 ranged from 2.7 to 4.0 hours in those subjects who had better response with esomeprazole *versus* comparator, and from 0.9 to 2.4 hours for those who had better response with comparator PPIs *versus* esomeprazole (Table 3). The better median response of gastric pH and lower rate of incomplete response for esomeprazole *versus* pantoprazole and lansoprazole are also illustrated in Figure 2b, and Figure 2c and d, respectively.

Discussion

The current analyses of four randomized, controlled trials of PPIs demonstrate that treatment with esomeprazole 20 mg maintained intragastric pH >4 for more than half of the 14-hour daytime awake period, despite food-stimulated acid

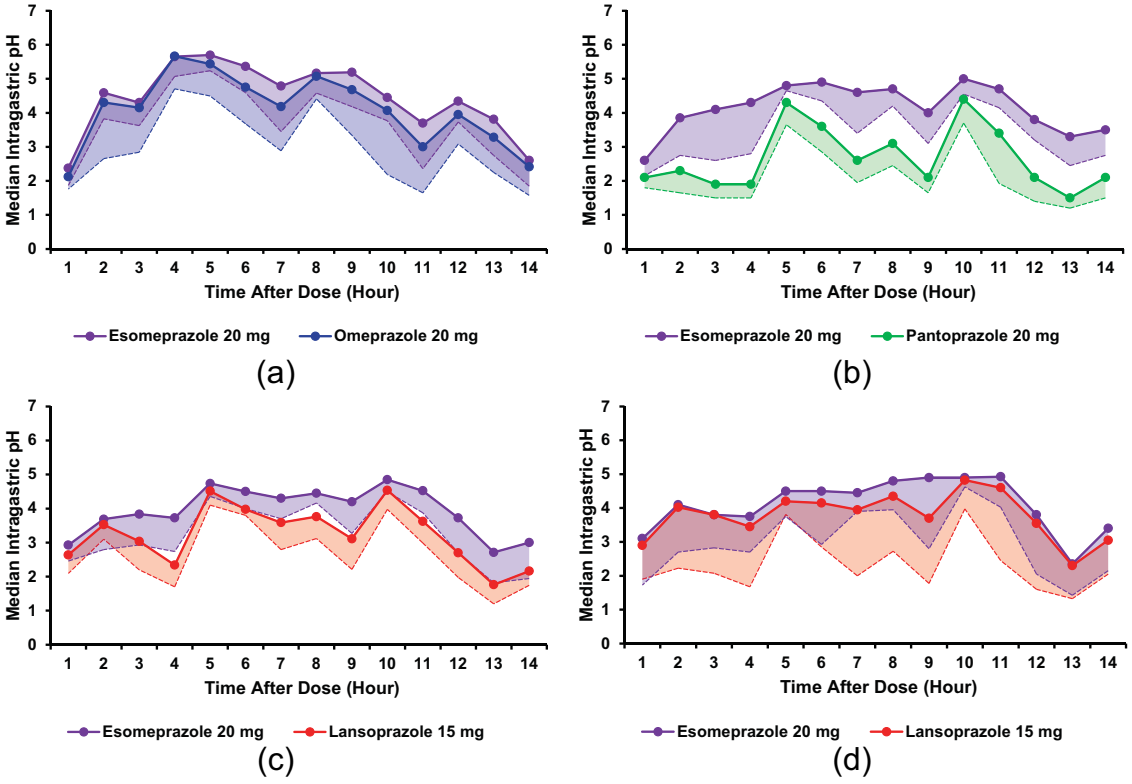

Figure 2. Graphs of 14-hour median intragastric pH on day 5 of dosing with esomeprazole 20 mg *versus*: (a) omeprazole 20 mg; (b) pantoprazole 20 mg; (c) lansoprazole 15 mg; and (d) lansoprazole 15 mg. Solid lines represent the median values; dotted lines represent the 25th percentile; and shaded areas represent the spread of values between the 50th and 25th percentile values.

secretion and postprandial reflux. Importantly, esomeprazole 20 mg provided intragastric acid suppression for a significantly greater percentage of the 14-hour daytime awake period than was achieved with currently approved OTC doses of the PPI comparators including omeprazole, pantoprazole and lansoprazole. Analyses of the median and 25th percentile intragastric pH across the 14-hour daytime awake period demonstrate the variability of response within the population. The results suggest that there are fewer patients at risk of an incomplete response or 'under-response' with esomeprazole 20 mg relative to the PPI comparators due to less than adequate acid control. These data are clinically relevant because poor control of acid reflux can contribute to the failure of PPI therapy in GERD patients.

Analyses of individual responses to PPI treatment in the 14-hour daytime awake period showed that the large majority of subjects in all 4 studies had a superior response to acid suppression with esomeprazole 20 mg *versus* the PPI comparators at OTC dosages, providing these subjects with 2.7–4.0 additional hours with adequate acid control relative to the comparators across the daytime awake period.

The superior acid control observed with esomeprazole 20 mg relative to that with omeprazole 20 mg is expected. Esomeprazole is the *S*-isomer of the racemate omeprazole, and is subjected to a slower elimination and less influenced by CYP2C19 (the main CYP450 metabolizing enzyme for all the studied PPIs) polymorphism than omeprazole, resulting in a higher and less variable area under the plasma concentration curve when given at the same dose [Andersson *et al.* 2001]. The superior acid control observed with esomeprazole 20 mg relative to that with the other studied PPI comparators may be attributable to differences in potency.

In a meta-analysis of 57 clinical studies measuring effects of PPIs on gastric acid control in relation to drug and dose, integrated population pharmacokinetic modeling was used to generate clinically comparative dosages [Kirchheiner *et al.*

Table 3. Individual responses to acid suppression on esomeprazole 20 mg *versus* the proton-pump inhibitor comparator during the 14-hour daytime period.*$

Treatment comparison	Study 1		Study 2		Study 3		Study 4	
	Esomeprazole 20 mg *versus* omeprazole 20 mg ($n = 36$)		Esomeprazole 20 mg *versus* pantoprazole 20 mg ($n = 35$)		Esomeprazole 20 mg *versus* lansoprazole 15 mg ($n = 36$)		Esomeprazole 20 mg *versus* lansoprazole 15 mg ($n = 26$)	
	Proportion of subjects (%) (95% CI)	*Mean gain in time with pH > 4 (hours)*	*Proportion of subjects (%) (95% CI)*	*Mean gain in time with pH > 4 (hours)*	*Proportion of subjects (%) (95% CI)*	*Mean gain in time with pH > 4 (hours)*	*Proportion of subjects (%) (95% CI)*	*Mean gain in time with pH >4 (hours)*
Better response* on esomeprazole	75.0 (57.8–88.9)	2.7	97.1 (85.1–99.9)	4.0	86.1 (70.5–95.3)	3.5	69.2 (48.2–85.7)	3.1
Better response* on comparator	25.0 (12.1–42.2)	2.4	2.9 (0.1–14.9)	0.9	13.9 (4.7–29.5)	1.3	30.8 (14.3–48.5)	2.0
p value‡	0.0027		< 0.0001		< 0.0001		0.0499	

*Better acid suppression response defined as more time with pH >4 in 14-hour daytime period.
$Analyses include subjects with data on both treatments of interest.
‡Test for H0: proportion = 0.5.
CI, confidence interval.

2009]. The doses of pantoprazole, lansoprazole, omeprazole, esomeprazole and rabeprazole needed to achieve a mean 24-hour intragastric pH of 4 were estimated to be 89.2 mg, 22.6 mg, 20.2 mg, 12.6 mg and 11.1 mg, respectively, in healthy volunteers and 166 mg, 41.8 mg, 37.7 mg, 23.6 mg and 20.7 mg, respectively, in GERD patients. These findings are in line with the results of the current analyses.

The primary goal of studies of intragastric acidity has typically been to measure intragastric pH data across an entire 24-hour period rather than just the daytime period [Katz and Johnson, 2011]. These data extend the previously published literature by evaluating acid control specifically during the 14-hour daytime, typically the awake period of the 24-hour cycle. Assessment of acid control across the daytime awake period may prove to be a more relevant predictor of symptom control efficacy in GERD sufferers who use OTC PPIs for short-term relief of heartburn caused by acid reflux since a large majority of this population will have milder GERD [Venables *et al.* 1997]. In this group, reflux occurs predominantly postprandially, with generally low levels of esophageal acid exposure during the nighttime hours [Dent, 1994].

Because the majority of reflux symptoms occur during waking hours, we postulate that better control of daytime intragastric pH should be the key aim in most mild GERD patients and that this should translate into improved treatment of acid-related inflammation and sensitization of the esophagus, along with their associated symptoms, including nighttime symptoms. Effective daytime control of gastric pH may also translate into reduced nighttime symptoms and improved sleep quality [Johnson *et al.* 2005, 2010] by reduction of acid reflux-induced esophageal mucosal sensitization. The data on the timing of reflux and its associated symptoms in the great majority of GERD patients with milder disease indicate that, from the perspective of the efficacy of therapy, it is most logical to focus on acid control during the 14-hour daytime awake period for self-directed use of PPIs in the OTC setting.

Conclusion

Across the 14-hour daytime period, esomeprazole 20 mg provided acid control for a significantly greater average proportion of time *versus* the PPI comparators omeprazole, pantoprazole and lansoprazole at OTC doses. More patients achieved

a superior response and fewer patients had an incomplete response during acid suppression with esomeprazole 20 mg relative to omeprazole 20 mg, pantoprazole 20 mg and lansoprazole 15 mg. Because the major burden of reflux episodes occurs during the daytime awake period, improved control of daytime intragastric pH may lessen the overall acid-related inflammation and sensitization of the esophagus and thereby translate to better symptomatic control of the frequent acid reflux symptoms that are often managed in the OTC setting.

Funding

All studies were funded by AstraZeneca, which entered into an agreement with Pfizer for the over-the-counter (OTC) rights for NEXIUM® (esomeprazole magnesium). Medical writing support was provided by Diane Sloan, PharmD, of Peloton Advantage, LLC, and was funded by Pfizer.

Conflict of interest statement

P.K. has served as a consultant for Ironwood Pharmaceuticals and Pfizer Consumer Healthcare. He has received an honorarium from Takeda Pharmaceutical Co. Ltd. He has received honoraria from AstraZeneca and Pfizer in connection with the development of this manuscript.

P.J.K. has served as a consultant for AstraZeneca, GlaxoSmithKline, Pfizer and Trimedyne Inc. and has served as advisory board member for Reckitt Benckiser. He has received honoraria from AstraZeneca and Pfizer in connection with the development of this manuscript.

D.A.J. has served as a speaker for Takeda Pharmaceutical Co. Ltd, as a consultant for Medigus Ltd, Pfizer and Takeda, and has received honoraria from AstraZeneca and Takeda Pharmaceutical Co. Ltd. He has also served as advisory board member for Janssen Pharmaceutical, Pfizer, Takeda Pharmaceutical Co. Ltd and WebMD/Medscape. He has received honoraria from AstraZeneca and Pfizer in connection with the development of this manuscript.

T.L. is a former employee of AstraZeneca. He has no other potential conflicts of interest to declare.

K.R. is a former employee of AstraZeneca. She has no other potential conflicts of interest to declare.

B.T. is an employee of AstraZeneca. He owns stocks and shares in AstraZeneca.

V.H. is an employee of Pfizer.

J.D. has served as a speaker and a consultant for AstraZeneca and Pfizer. He has received honoraria from AstraZeneca and Pfizer in connection with the development of this manuscript.

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