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Review article: gastric acidity – comparison of esomeprazole with other proton pump inhibitors

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SUMMARY

Gastric acid suppression is the most effective medical therapy to control acidic gastro-oesophageal reflux: individuals in whom therapy fails usually have inadequate acid suppression. Twenty-four-hour intragastric pH-metry measures the percentage of time that gastric pH is above 4 or 3, the critical thresholds for tissue damage and symptom generation in the distal oesophagus. Effective medical therapy must control gastric acidity throughout the daytime, including the postprandial period. It is therefore useful to report the percentage of patients in whom gastric acidity is controlled above pH 4 for at least 16 out of 24 h. Esomeprazole was compared with standard-dose proton pump inhibitors in healthy volunteers and patients with gastro-oesophageal reflux disease. Esomeprazole, 40 mg daily, was significantly more effective at controlling gastric acidity above pH 4 for more than 16 h than lansoprazole, 30 mg daily (38% of individuals vs. 5%, respectively). Esomeprazole, 40 mg daily, also suppressed gastric acidity more effectively and in more individuals than pantoprazole, 40 mg daily, and rabeprazole, 20 mg daily. Esomeprazole, 20 mg daily, was significantly more effective at controlling gastric acidity than lansoprazole, 15 mg daily. The improved acid control with esomeprazole compared with other proton pump inhibitors is likely to result in superior healing rates and improved symptom relief, with fewer therapy-resistant patients.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a condition comprising disturbed motility of the proximal gastrointestinal tract, resulting in exposure of the oesophageal mucosa to acid-peptic refluxate from the stomach. Prokinetic drugs, at the present state of development, have been ineffective in GERD therapy.[1, 2] Pharmacological suppression of gastric acidity has proved effective in symptom control and healing of reflux oesophagitis, and particularly so after the introduction of omeprazole and later proton pump inhibitors. In some countries, four different proton pump inhibitors (omeprazole, lansoprazole, pantoprazole and rabeprazole) have been available for routine prescription to patients.

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Proton pump inhibitors act by bonding covalently to the amino acid cysteine 813 present at their primary binding site on the proton pump molecule on the luminal surface of gastric parietal cells. This results in irreversible inhibition of acid secretion from the gastric H^+,K^+-ATPase molecule, and only after recruiting newly synthesized proton pump molecules from the Golgi apparatus of the cell does acid secretion gradually resume. As proton pump inhibitors block the final step in the pathway to gastric acid secretion, they are effective against both basal and stimulated acid secretion, and whether stimulation is pharmacological or induced by a meal.[3] Proton pump inhibitors are most effective against meal-induced gastric acid secretion.

Esomeprazole is the latest proton pump inhibitor, and was developed as the S-isomer of omeprazole to improve on the pharmacokinetic properties of its predecessor. It

has been shown to be more potent than omeprazole in suppressing gastric acidity and is effective in short- and long-term therapy of GERD.[4–6]

PATTERNS OF GASTRO-OESOPHAGEAL REFLUX IN PATIENTS WITH GERD

When treating patients with GERD with acid-suppressive medication it is crucial that gastric acidity is adequately inhibited, both in terms of elevation of gastric pH and the duration of time during which pH is elevated.

When Johnsson *et al*. studied 80 patients with GERD with 24-h intraoesophageal pH-metry,[7] they found that oesophageal acid exposure occurred mainly after meals, and particularly after dinner. Nocturnal acid exposure was much less pronounced in this group of patients, and the majority was within normal limits. This pattern was also reflected in symptom episodes of GERD, which also occurred mainly after meals (71%), and particularly after dinner (31%). Only 11% of symptom episodes occurred in the recumbent position and mostly during the first 2 h of the night. These findings provide a good rationale for administering proton pump inhibitors in the morning before breakfast. It is, however, also important that the duration of action should be at least 12–16 h, to avoid acid reflux after dinner and on going to bed.

In patients with moderate-to-severe GERD, acid reflux can occur at any time during the 24 h, and with increasing severity of disease it becomes important to control gastric acidity throughout the day and night.

IMPORTANCE OF GASTRIC ACID CONTROL

There is indirect evidence to indicate that healing of reflux oesophagitis is directly related to the number of hours out of 24 that gastric pH is elevated above 4. pH 4 is a critical threshold, above which neither tissue damage[8] nor symptoms[9] are likely to be elicited by refluxate reaching the distal oesophagus. Bell *et al*. correlated healing rates of reflux oesophagitis with what was known about acid suppression with omeprazole, H_2-receptor antagonists and antacids, and found an approximately linear relationship between healing rate and the number of hours out of 24 for which gastric pH was controlled above 4.[10] Similar associations have been found for healing of duodenal ulcers.

Contrary to what we often expect, gastric acid suppression is not always effective with standard doses of the proton pump inhibitors that have been available for clinical use. Figure 1 shows a tracing of oesophageal and gastric pH in a patient treated with a standard dose of a proton pump inhibitor once daily before breakfast. We can see how gastric pH is elevated after each meal, although there are also periods during the day with high intragastric acidity. During these periods, severe gastro-oesophageal reflux occurs. After dinner, gastric pH falls and stays low throughout the night. Failure to control gastric acidity during the night, so-called nocturnal acid breakthrough, is a common reason for treatment failure in patients with severe reflux disease.[11]

There are important interindividual differences in the acid-suppressive response to proton pump inhibitors, as has been shown in several studies. Even with twice-daily dosing of omeprazole or lansoprazole, the response can vary from excellent to almost none, depending on factors such as *Helicobacter pylori* status, age, gender, smoking and genetic differences in hepatic metabolism. The improved pharmacokinetic profile of esomeprazole compared with omeprazole has markedly reduced this problem with commonly used doses.[12]

INTERPRETATION OF 24-H INTRAGASTRIC pH-METRY IN A CLINICAL SETTING

The introduction of microelectronic dataloggers and suitable software has made 24-h monitoring of not only

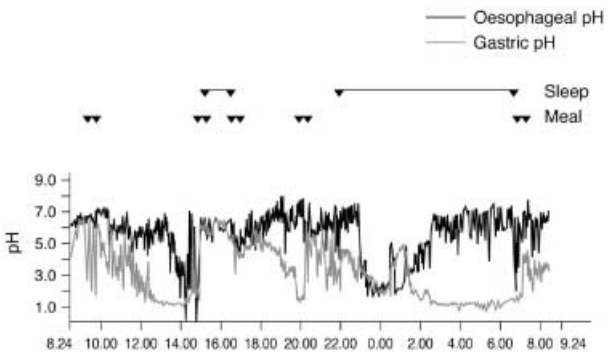

Figure 1. Oesophageal and gastric pH in a patient with reflux oesophagitis, during treatment with a standard dose of a proton pump inhibitor once daily before breakfast, who continued to have occasional symptoms after dinner and in whom the oesophagitis did not heal. The tracing shows failure of the medication to control gastric acidity in the evening and during the night. There is considerable acidic gastro-oesophageal reflux during periods of high gastric acidity.

intraoesophageal but also intragastric acidity available for clinical and research purposes. Concomitant recording of pH at these two levels gives a clear understanding of how acidification of the gastric contents may lead to intermittent gastro-oesophageal reflux in predisposed individuals with a functionally incompetent cardia.

When comparing acid-suppressive agents at different doses, group data have been expressed in various ways. Traditionally, either the area under the curve (AUC) for the 24-h H^+ profile or the median 24-h intragastric pH value have been used. The AUC value is very sensitive to even small changes in acidity, but is also sensitive to errors and is complicated to interpret and use, whereas the latter variable has proved relatively insensitive.[13] Median or mean fraction of time for which gastric pH is above (or below) a threshold of 3 or 4 has been used more in recent years, and is relatively sensitive to even minor changes in duration of gastric acidification, which, although short-lasting, can result in detrimental gastro-oesophageal reflux. This variable is similar to how we express oesophageal acid exposure as the percentage of time that the oesophageal pH is below 4, which makes the relationship between gastric and oesophageal acidification easy to understand.

A clinically important measure of efficacy with proton pump inhibitors, due to the pronounced interindividual variation in gastric acidity during therapy, is the comparison of proportions of individuals in whom gastric pH is controlled above 4 for more than 12 or 16 h out of the 24-h period. This tends to indicate sufficient acid control after meals, including dinner, and even in the early hours of the night. This inevitably results in better clinical results and fewer therapy-resistant patients, and should therefore also suggest improved resource utilization.

METHODOLOGY OF GASTRIC ACIDITY STUDIES

Recently, acid control with esomeprazole has been compared with that of other proton pump inhibitors in a number of crossover pharmacodynamic studies in either patients with GERD or in healthy individuals. The designs of these studies were very similar.[12] In all the studies, individuals were *H. pylori*-negative. Individuals received study medication in the morning, 30 min before breakfast, for two periods of 1 or 5 days, separated by at least 13 days of washout. Gastric acidity was recorded on Days 1 and/or 5 in order to evaluate the immediate and steady-state effects of medication on the gastric acidity profile, respectively. A pH-sensitive glass electrode was inserted into the proximal stomach and data were sampled at a frequency of 0.25–0.10 Hz. The glass electrodes were calibrated at two points prior to and immediately after each recording, to compensate for any drift. Data were stored in a solid-state datalogger, and later transferred to a computer and analysed with dedicated software. Meals were standardized to reduce variation due to factors other than the drug and dosage used. Healthy individuals tended to be younger than patients, which may influence the effect achieved, but is usually considered acceptable in studies of this type.

COMPARATIVE STUDIES OF ESOMEPRAZOLE WITH OTHER PROTON PUMP INHIBITORS

Thomson *et al.*[14] and Röhss *et al.*[15] in two separate studies compared esomeprazole, 40 mg once daily, with lansoprazole, 30 mg once daily, which are the approved healing doses of both drugs in patients with reflux oesophagitis. The first study was performed in 28 healthy individuals and was a single-dose study, which showed esomeprazole to be significantly more effective than lansoprazole, with a difference in percentage of time that gastric pH was above 4 of 5.5% (95% CI 1.8–9.1) (Table 1).[14] The other study involved 20 healthy individuals and was a multiple-dose study with pH-metry performed on Day 5 of medication.[15] These data are more relevant for comparing the efficacy of chronic therapy, and showed that esomeprazole was again significantly superior to lansoprazole in terms of percentage of time that gastric pH was above 4, with a numerical difference of 12.4% (95% CI 7.4–17.5). Even more important in the practical care of patients, the proportion of individuals with gastric pH controlled above 4 for more than 12 or 16 h was clearly higher with esomeprazole (Table 2).

Wilder-Smith *et al.* reported a similar study, which compared esomeprazole, 40 mg once daily, and pantoprazole, 40 mg once daily, taken in the morning before breakfast.[16] This study included 31 relatively young patients with chronic mild-to-moderate symptoms of GERD, and intragastric pH-metry was performed on both Days 1 and 5. Day 1 data showed that esomeprazole was significantly more effective than pantoprazole in terms of the percentage of time that gastric pH was above 4, with a difference of 21.2% (95% CI 14.9–27.4) (Table 1). By Day 5, the effect of both medications had improved further (Table 1), but

Table 1. Gastric acidity, expressed as the percentage of time that gastric pH is above 4, on Days 1 and 5 in individuals treated with esomeprazole, lansoprazole, pantoprazole and rabeprazole in crossover pharmacodynamic studies

		Day 1		Day 5	
		Percentage time gastric pH >4	Mean difference (95% CI)	Percentage time gastric pH >4	Mean difference (95% CI)
Thomson *et al.*[14]	Esomeprazole, 40 mg once daily	57.2	5.5 (1.8–9.1)		
	Lansoprazole, 30 mg once daily	51.8			
Röhss *et al.*[15]	Esomeprazole, 40 mg once daily			65.4	12.4 (7.4–17.5)
	Lansoprazole, 30 mg once daily			53.0	
Wilder-Smith *et al.*[16]	Esomeprazole, 40 mg once daily	50.4	21.2 (14.9–27.4)	66.5	22.3 (18.8–25.9)
	Pantoprazole, 40 mg once daily	29.2		44.2	
Wilder-Smith *et al.*[17]	Esomeprazole, 40 mg once daily			61.0	15.8 (5.4–26.3)
	Rabeprazole, 20 mg once daily			45.1	
Wilder-Smith *et al.*[18]	Esomeprazole, 40 mg once daily	41.0	11.6 (4.5–18.7)	59.4	14.8 (8.1–21.6)
	Rabeprazole, 20 mg once daily	29.4		44.5	
Wilder-Smith *et al.*[19]	Esomeprazole, 20 mg once daily			50.4	7.4 (1.0–13.8)
	Lansoprazole, 15 mg once daily			43.0	

Table 2. Proportions of individuals in whom gastric acidity was controlled above pH 4 for more than 12 and more than 16 out of 24 h on Days 1 and 5 of dosing with esomeprazole, lansoprazole, pantoprazole and rabeprazole in crossover pharmacodynamic studies

		Day 1		Day 5	
		Percentage individuals with gastric pH >4 for >12 h	Percentage individuals with gastric pH >4 for >16 h	Percentage individuals with gastric pH >4 for >12 h	Percentage individuals with gastric pH >4 for >16 h
Thomson *et al.*[14]	Esomeprazole, 40 mg once daily	71	36		
	Lansoprazole, 30 mg once daily	61	21		
Röhss *et al.*[15]	Esomeprazole, 40 mg once daily			90	38
	Lansoprazole, 30 mg once daily			57	5
Wilder-Smith *et al.*[16]	Esomeprazole, 40 mg once daily	39	26	90	50
	Pantoprazole, 40 mg once daily	10	3	30	10
Wilder-Smith *et al.*[17]	Esomeprazole, 40 mg once daily			77	32
	Rabeprazole, 20 mg once daily			36	5
Wilder-Smith *et al.*[18]	Esomeprazole, 40 mg once daily	39	12	76	33
	Rabeprazole, 20 mg once daily	6	3	39	12
Wilder-Smith *et al.*[19]	Esomeprazole, 20 mg once daily			50	23
	Lansoprazole, 15 mg once daily			35	15

esomeprazole was still significantly superior, with a mean difference of 22.3% (95% CI 18.8–25.9). Many more patients achieved the goal of having gastric pH controlled above 4 for more than 12 and more than 16 h with esomeprazole, both on Days 1 and 5 (Table 2). Figure 2 shows the median gastric pH during six 4-h periods of the day and night on Days 1 and 5 of treatment. On both days, esomeprazole, 40 mg once daily, provided superior control of gastric acidity throughout the important hours of the day.

Esomeprazole, 40 mg once daily, and rabeprazole, 20 mg once daily, before breakfast were compared in two separate studies. The first study was performed in 22 healthy individuals in whom intragastric pH-metry was performed on Day 5 only.[17] The mean difference was 15.8% (95% CI 5.4–26.3) in favour of esomeprazole

(Table 1). Many more individuals reached the goal of having gastric pH controlled above 4 for more than 12 and more than 16 h with esomeprazole (Table 2). The second study included 34 patients with chronic mild-to-moderate symptoms of GERD.[18] Twenty-four-hour intragastric pH-metry was performed on both Days 1 and 5 (Table 1). Esomeprazole was found to be significantly superior to rabeprazole in the percentage of time that gastric pH was above 4 (Table 1), with a mean difference of 11.6% (95% CI 4.5–18.7) on Day 1 and 14.8% (95% CI 8.1–21.6) on Day 5.

Esomeprazole, 20 mg once daily, and lansoprazole, 15 mg once daily, are the approved doses for maintenance therapy in patients with reflux oesophagitis and for endoscopy-negative GERD. Wilder-Smith *et al.* compared the control of gastric acidity achieved with these lower doses of the drugs in 27 healthy individuals when taken once daily before breakfast.[19] They found esomeprazole to be significantly more effective than lansoprazole on Day 5, with a mean difference in the percentage of time that gastric pH was above 4 of 7.4% (95% CI 1.0–13.8) (Table 1). More importantly, gastric pH was controlled above 4 for more than 12 and 16 h in more patients receiving esomeprazole than lansoprazole (Table 2).

These findings are summarized in Figure 3, showing the proportions of patients in whom gastric acidity is controlled above pH 4 for 16 h or more, which may be the ultimate goal when treating patients with moderate-to-severe GERD.

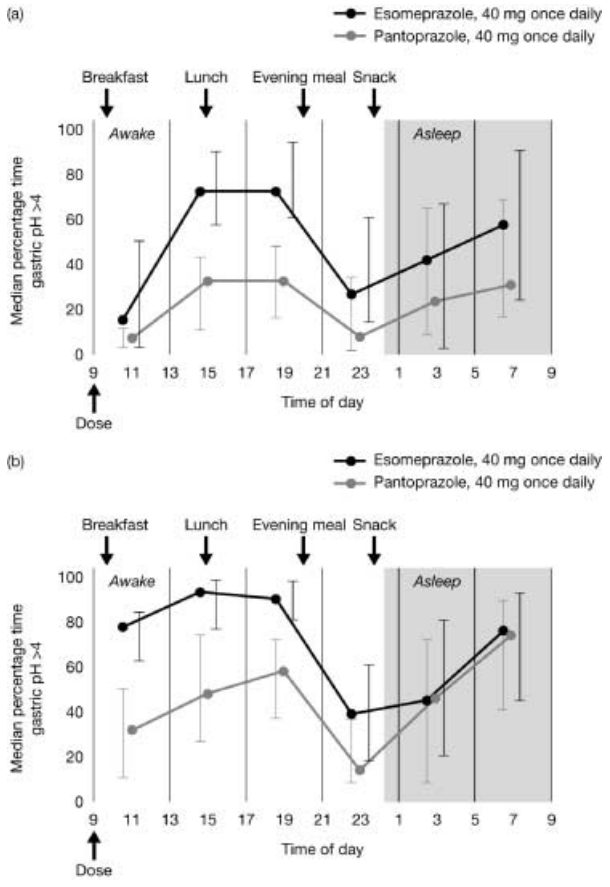

Figure 2. Median gastric pH during six 4-h periods of the day and night in 31 patients with gastro-oesophageal reflux disease who were treated with esomeprazole, 40 mg once daily, or pantoprazole, 40 mg once daily, for two periods of 5 days in randomized order, separated by at least 13 days of washout. (a) Gastric pH on Day 1 of medication; (b) gastric pH on Day 5 of medication. The interquartile range during each period is shown within brackets. On both days, the median gastric pH during the day was highest when taking esomeprazole. The Day 5 curves show smaller interindividual variation with esomeprazole. On Days 1 and 5, more than 75% of patients were better treated during the daytime when receiving esomeprazole, than 75% of patients when treated with pantoprazole.[16]

CONCLUSIONS

Crossover studies of gastric pH in patients and healthy individuals have shown esomeprazole, 40 mg once daily, to be significantly more effective than commonly approved doses of other proton pump inhibitors, on both Days 1 and 5 of medication. Comparing the proportions of patients in whom gastric acidity is controlled above pH 4 is particularly useful in the clinical setting, due to important interindividual variation in response to all proton pump inhibitors. This shows esomeprazole, 40 mg once daily, to control

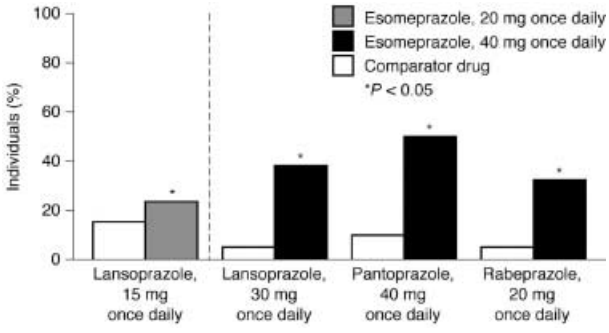

Figure 3. Percentage of individuals treated with esomeprazole, lansoprazole, pantoprazole and rabeprazole in four crossover pharmacodynamic studies, in whom gastric pH was above 4 for 16 h or more out of 24 h (Day 5 data).[15–17, 19]

gastric acidity in significantly more patients than other proton pump inhibitors at approved healing doses. A recent study showed esomeprazole, 20 mg once daily, to be more effective and control gastric pH above 4 in more individuals than lansoprazole, 15 mg once daily, the doses approved for the maintenance therapy of GERD. The improved gastric acid control seen with esomeprazole is likely to explain the superior healing rates and improved symptom relief in patients with GERD, with fewer therapy-resistant patients.

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