Aliment Pharmacol Ther 2003; 17 (Suppl. 1): 5–9.

Review article: pharmacology of esomeprazole and comparisons with omeprazole

J. DENT
Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital, Adelaide, Australia

SUMMARY

Plasma concentration measurements have confirmed that the advantageous hepatic metabolism of esomeprazole results in a greater delivery of acid suppressant to the systemic circulation, compared with an equal dose of omeprazole. Also, this superior delivery has been shown to cause a more consistent and greater suppression of pentagastrin-stimulated gastric acid secretion by esomeprazole, 20 mg, compared with omeprazole, 20 mg. The superior acid-suppressant properties of esomeprazole have been revealed by extensive 24-h intragastric pH-monitoring studies. Compared with omeprazole, 20 mg, esomeprazole, 20 mg and 40 mg, has been shown to give superior outcomes on three key measures of antisecretory effect: (1) consistency amongst individuals; (2) duration over the 24-h cycle; (3) overall impact on pH. As there is a substantial increment of acid control from esomeprazole, 20 mg, to esomeprazole, 40 mg, this latter dose is the most appropriate to investigate for modern initial therapy of reflux disease, with the aim of achieving the highest possible response rates in the shortest possible time.

AREA UNDER THE PLASMA CONCENTRATION–TIME CURVE

The studies on the hepatic metabolism of esomeprazole described in the previous article predict that orally administered S-omeprazole – that is, esomeprazole – would give a higher peak of the serum concentration when compared with an equal dose of either the racemic mixture of the currently marketed omeprazole preparations or R-omeprazole. This has been confirmed by measurements in healthy individuals[1] and in patients with reflux disease.[2]

Figure 1 shows the plasma concentration–time curves after oral intake of omeprazole, 20 mg once daily, and esomeprazole, 20 mg and 40 mg once daily, on Day 5.[2] By Day 5, a steady state has been reached, so these data are also representative of longer periods of daily therapy. The plasma concentration–time curves show that use of esomeprazole, 20 mg, results in a substantial increase in the amount of drug that reaches the systemic circulation when compared with omeprazole, 20 mg.

The amount of drug delivered to the systemic circulation is best measured as the area under the plasma concentration–time curve (plasma AUC). The functional relevance of this measure is supported by a wealth of evidence, which shows that the effect of a proton pump inhibitor on acid secretion is related directly to the plasma AUC. This is to be expected, as the plasma AUC is a direct indication of the amount of drug that has reached the systemic circulation and so is available for binding to proton pumps in the parietal cell.[3]

It is important to note that hepatocytes 'see' the two optical isomers of omeprazole differently. Despite the substantially different metabolism of the isomers by hepatocytes, the parietal cell proton pumps are equally susceptible to blockage by these isomers.[1] This fact underpins the differences between esomeprazole and omeprazole when given orally.

Correspondence to: Professor J. Dent, Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital, Adelaide, SA 5000, Australia.
E-mail: jdent@mail.rah.sa.gov.au

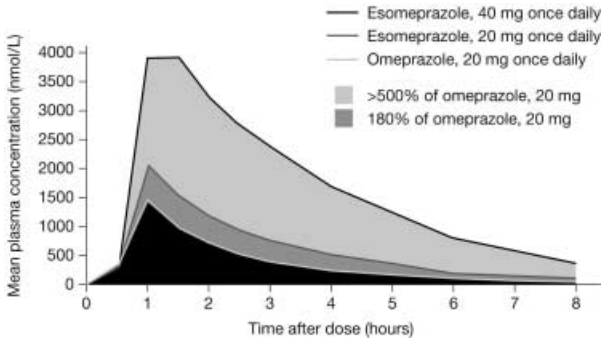

Figure 1. Plasma concentration curves for R- and S-omeprazole (esomeprazole) combined on Day 5 following oral once-daily intake. Data are from 36 patients studied three times each.[2]

When the plasma concentration–time curves shown in Figure 1 are converted to plasma AUC values, that for esomeprazole, 20 mg, is about 180% of that for omeprazole, 20 mg. Even more impressive, the plasma AUC for esomeprazole, 40 mg, is more than 500% greater than that for omeprazole, 20 mg. The reasons for this nonlinear increase of systemic bioavailability are not fully understood, but it has substantial potential benefit.

CLINICALLY RELEVANT BENCHMARKS OF EFFECT ON ACID SECRETION FOR THE TREATMENT OF REFLUX DISEASE

It is best to consider this before assessment of the data on the effects of esomeprazole on gastric acid secretion. There are three major variables that need to be considered:

- magnitude of effect on acid secretion
- consistency of this effect amongst individuals
- the duration over which the desired effect is maintained.

Much has been learnt about these variables over the last 20 years with regard to reflux disease. The minimum levels of effect on acid secretion required for consistent success of treatment of reflux disease are much greater than those needed for chronic peptic ulcer disease – these are clearly different diseases that need different therapeutic approaches.

Magnitude of effect on acid secretion

Animal models and studies *in vitro*[4] and extensive clinical data[5] indicate that, if the pH of the gastric content is raised above 4, this becomes minimally injurious to the oesophageal mucosa, with the attendant benefits of reliable healing of reflux oesophagitis and relief of reflux-induced symptoms.[6] Thus, elevation of gastric pH to above 4 is a major, validated benchmark.

Consistency of effect amongst individuals

This important measure has not been adequately appreciated in the past. First-generation proton pump inhibitors attain and surpass the benchmark of pH 4 at standard dosage if median intragastric pH is taken as the measure of effect.[7] This is shown in Figure 2 for omeprazole, and tells us that more than half of the patients studied achieve this major therapeutic benchmark, consistent with the high success rates of proton pump inhibitors for the treatment of reflux disease.

The median pH curve is uninformative about the 50% of patients whose intragastric pH is below the median pH value. It is the patients within this sub-group in whom proton pump inhibitor therapy for reflux oesophagitis fails. Several oesophageal pH-monitoring studies have shown that failure of proton pump inhibitor therapy is associated with persistence of excessive numbers of gastro-oesophageal reflux episodes with a pH of less than 4 during proton pump inhibitor therapy at standard dose.[6, 8]

The persistence of acid reflux in a minority of patients during first-generation proton pump inhibitor therapy at standard dosage underscores the fact that there is substantial variation of the gastric antisecretory response to proton pump inhibitor therapy. Patients who have a particularly small response of intragastric

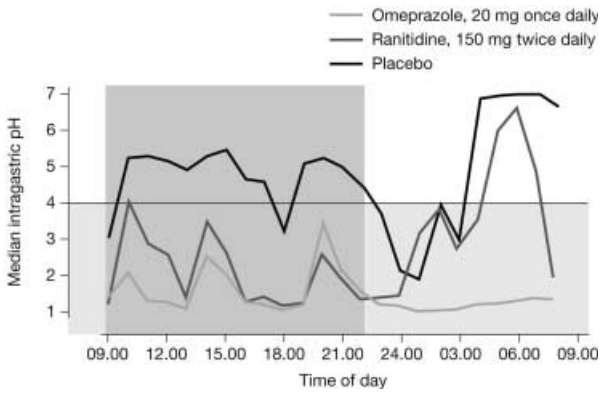

Figure 2. Hourly median intragastric pH in patients with duodenal ulcer. Data are for Day 28 of dosing with omeprazole, 20 mg once daily, compared with paired placebo studies.[7]

pH to proton pump inhibitor therapy are those in whom treatment is likely to fail.

Duration of elevation of gastric pH above 4

This third variable is also important, because, if the benchmark of gastric pH greater than 4 is only achieved for a small fraction of the 16 h of awake time, then therapeutic success is unlikely, on the basis of the patterning of reflux episodes over the 24-h cycle.

Patterns of gastro-oesophageal reflux over the 24-h cycle are illustrated in Figure 3 for a mixed population of oesophagitis and endoscopy-negative patients.[9] These data can therefore be considered representative for 'mainstream' reflux patients – that is, the patient mix encountered outside the problem group referred to gastroenterologists for further assessment. Figure 3 shows clearly that acidic gastro-oesophageal reflux occurs predominantly during the hours of wakefulness, and is driven by food intake. This insight contradicts previous assumptions about the time patterns of reflux reached before pH-monitoring made it possible to measure reflux patterns directly over a 24-h period.

It should be noted that there are exceptions to the time patterning of reflux shown in Figure 3, as these are mean data. Significant sleep-time reflux occurs in a proportion of patients, predominantly those with severe or very severe reflux oesophagitis (Los Angeles Grades C and D).[10, 11]

The time patterning of reflux (Figure 3) defines the primary target time-window for elevation of intragastric pH to greater than 4. This is the period of wakefulness. Given the amount of reflux that occurs after the evening meal, it appears that the greatest success would be achieved with an agent and dose that has a major impact on gastric pH for around 16 h after morning dosing.

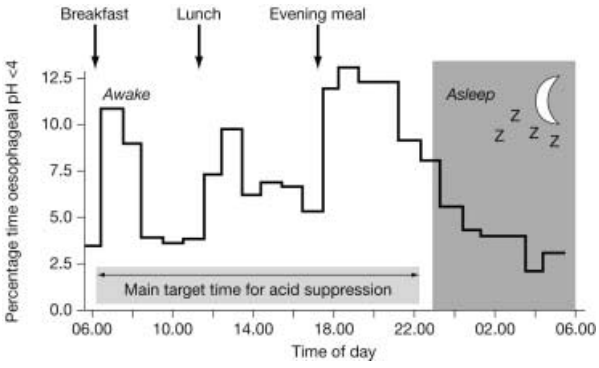

Figure 3. Mean hourly patterns of gastro-oesophageal reflux over the 24-h cycle in a mixed group of oesophagitis and endoscopy-negative patients, showing that daytime, postprandial reflux is, overall, the most important target for therapy.[9] Figure reprinted from Johnsson *et al.* Timing of reflux symptoms and oesophageal acid exposure, Gullet, Volume 2, pp. 58–62, © 1992, with permission of the publisher Elsevier Science.

PENTAGASTRIN-STIMULATED GASTRIC ACID SECRETION – COMPARISON BETWEEN ESOMEPRAZOLE AND OMEPRAZOLE

A traditional study of pentagastrin-stimulated gastric acid secretion reveals the impacts of the favourable pattern of hepatic metabolism of esomeprazole.[12] Three studies were performed in each healthy individual on Day 5 of dosing with esomeprazole, omeprazole and placebo. The effects of esomeprazole and omeprazole were referenced to the amounts of acid aspirated during control studies when placebo was given.

The data shown in Figure 4 illustrate the variability of response to omeprazole, 20 mg once daily, and esomeprazole, 20 mg once daily.[3] With esomeprazole, the variability is much less and the mean magnitude of effect is significantly greater ($P = 0.01$).

TWENTY-FOUR-HOUR INTRAGASTRIC pH-MONITORING – COMPARISONS BETWEEN ESOMEPRAZOLE AND OMEPRAZOLE

Twenty-four-hour intragastric pH-monitoring has been used widely for comparisons of the effects of esomeprazole with omeprazole (see below) and other proton pump inhibitors (see Hatlebakk, this supplement[12]). This is the most suitable technique for this, as it yields

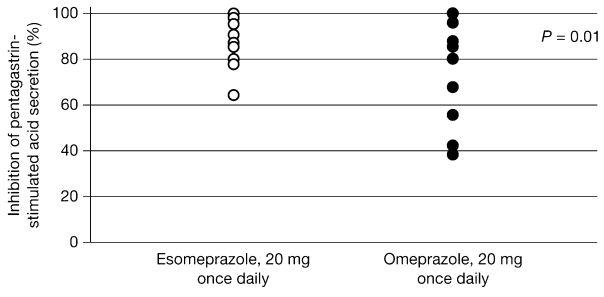

Figure 4. Effects of omeprazole, 20 mg once daily, and esomeprazole, 20 mg once daily, on maximal pentagastrin-stimulated gastric acid secretion, determined in the absence of acid inhibition. Esomeprazole, 20 mg once daily, resulted in more consistent secretory inhibition than omeprazole, 20 mg once daily.[3]

detailed data on clinically highly relevant measures of effect, the most important of these being magnitude, duration, variability and timing of effects on gastric pH (see above).

Reporting of outcomes of 24-h intragastric pH-monitoring studies should communicate effectively on the sub-group of outlier patients that responds least to acid suppression, in order to improve the prediction of clinical benefit in patients who respond poorly to first-generation proton pump inhibitors at standard dose. Accordingly, data are presented in this article with interquartile ranges, for four blocks of time over the 24-h period. In addition, the overall impact of therapy on intragastric pH is expressed as the percentage of patients who reach the benchmark of elevation of gastric pH above 4 for several fractions of the total 24-h cycle, as this measure is sensitive to the occurrence of a poor response to acid suppression.

Data for the pivotal comparison between omeprazole, 20 mg once daily, and esomeprazole, 40 mg once daily, are shown in Figures 5 and 6. This study was performed in 36 patients with reflux disease[2] and shows steady-state effects, as the measurements were made on Day 5 of therapy. The robustness of the data is enhanced by these being paired studies, performed in random order, with adequate time for washout of the first drug studied before the second study started.

Figure 5 shows the effects on pH according to time of day. Esomeprazole, 40 mg once daily, had a consistently superior effect, particularly during the major target time for therapy. Importantly, this superiority was evident as achievement of the benchmark elevation of pH 4 in a very high proportion of the patients, with this effect being quite well sustained for 16 h after drug ingestion. The larger interquartile ranges, lower median effects and shorter durations of effect of omeprazole, 20 mg once daily, are evident from Figure 5.

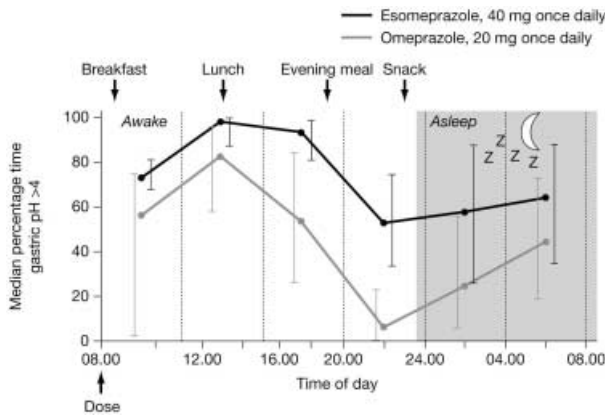

Figure 5. Effect of esomeprazole, 40 mg once daily, on median 4-hourly intragastric pH compared with omeprazole, 20 mg once daily, in 36 patients with reflux disease. The vertical bars show the interquartile ranges. The substantially greater and more consistent effect of esomeprazole, 40 mg once daily, can be seen compared with omeprazole, 20 mg once daily (data derived from[2]).

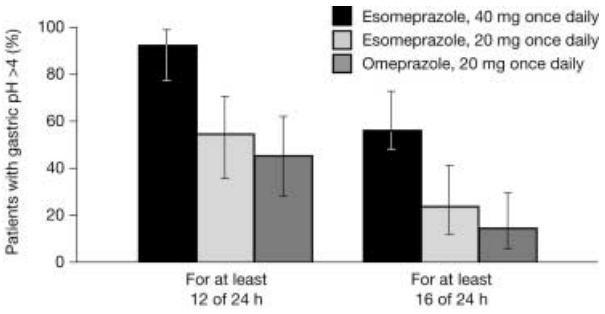

Figure 6. Intragastric pH data derived from,[2] expressed as the proportion of patients in whom gastric pH was above 4 for different durations of the 24-h cycle (Day 5 of dosing). The gain in acid control with esomeprazole, 40 mg once daily, for the entire patient group is well illustrated by this analysis method.

Data for the proportions of patients in whom gastric pH was above 4 for different durations of the 24 h are shown in Figure 6. Included in this figure are data from the comparison also made with esomeprazole, 20 mg once daily, within this study; this was also significantly superior to omeprazole, 20 mg once daily.[2]

CHOICE OF THE STANDARD DOSE OF ESOMEPRAZOLE FOR INITIAL THERAPY OF REFLUX DISEASE

Data have been presented above, which establish that a lower than average response of acid secretion to proton pump inhibitor therapy is the major cause for failure of initial treatment of reflux oesophagitis. The intragastric pH-monitoring data for esomeprazole, 20 mg once daily, show improvement over omeprazole, 20 mg once daily, but the esomeprazole, 40 mg once daily, intragastric pH data show a further convincing gain in control of gastric pH, with an impressive minimization of the rate of poor response for individual patients. Given current insights into the causes of failure and success of proton pump inhibitor therapy, these pH-monitoring data point clearly to the choice of

esomeprazole, 40 mg once daily in the morning, as the dose that holds greatest promise for useful enhancement of the efficacy of initial proton pump inhibitor therapy for reflux disease.

REFERENCES

1 Hassan-Alin M, Andersson T, Bredberg E, Röhss K. Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. Eur J Clin Pharmacol 2000; 56: 665–70.

2 Lind T, Rydberg L, Kylebäck A, *et al.* Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2000; 14: 861–7.

3 Andersson T, Röhss K, Bredberg E, Hassan-Alin M. Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. Aliment Pharmacol Ther 2001; 15: 1563–9.

4 Goldberg HI, Dodds WJ, Gee S, Montgomery C, Zboralske FF. Role of acid and pepsin in acute experimental oesophagitis. Gastroenterology 1969; 56: 223–30.

5 Chiba N, de Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in Grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology 1997; 112: 1798–810.

6 Holloway RH, Dent J, Narielvala F, Mackinnon A. Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis. Gut 1996; 38: 649–54.

7 Lanzon-Miller S, Pounder RE, Hamilton MR, *et al.* Twenty-four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Aliment Pharmacol Ther 1987; 1: 239–51.

8 Leite LP, Johnston BT, Just RJ, Castell DO. Persistent acid secretion during omeprazole therapy: a study of gastric acid profiles in patients demonstrating failure of omeprazole therapy. Am J Gastroenterol 1996; 91: 1527–31.

9 Johnsson L, Adloum W, Johnsson F, Joelsson B. Timing of reflux symptoms and esophageal acid exposure. Gullet 1992; 2: 58–62.

10 Robertson D, Aldersley M, Shepherd H, Smith CL. Patterns of acid reflux in complicated oesophagitis. Gut 1987; 28: 1484–8.

11 Adachi K, Fujishiro H, Katsube T, *et al.* Predominant nocturnal acid reflux in patients with Los Angeles grade C and D reflux esophagitis. J Gastroenterol Hepatol 2001; 16: 1191–6.

12 Hatlebakk JG. Review article: gastric acidity – comparison of esomeprazole with other proton pump inhibitors. Aliment Pharmacol Ther 2003; 17(Suppl. 1): 10–15.

