Pharmacological and pharmacodynamic essentials of H₂-receptor antagonists and proton pump inhibitors for the practising physician

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The suppression of gastric acid secretion with anti-secretory agents has been the mainstay of medical treatment for patients with acid-related disorders. Although the majority of Helicobacter pylori-related peptic ulcers can be healed with antibiotics, ulcer healing and symptom control can be significantly improved when antibiotics are given with anti-secretory agents, especially with a proton pump inhibitor. There is a dynamic relationship between the suppression of intragastric acidity and the healing of peptic ulcer and erosive oesophagitis and control of acid-related symptoms. The suppression of gastric acid secretion achieved with H₂-receptor antagonists has, however, proved to be suboptimal for effectively controlling acid-related disorders, especially for healing erosive oesophagitis and for the relief of reflux symptoms. H₂-receptor antagonists are also not effective in inhibiting meal-stimulated acid secretion, which is required for managing patients with erosive oesophagitis. Furthermore, the rapid development of tolerance to H₂-receptor antagonists and the rebound acid hypersecretion after the withdrawal of an H₂-receptor antagonist further limit their clinical use. Although low-dose H₂-receptor antagonists are currently available as over-the-counter medications for self-controlling acid-related symptoms, their pharmacology and pharmacodynamics have not been well studied, especially in the self-medicating population. Proton pump inhibitors have been proved to be very effective for suppressing intragastric acidity to all known stimuli, although variations exist in the rapidity of onset of action and the potency of acid inhibition after oral administration at the approved therapeutic doses, which may have important clinical implications for the treatment of gastro-oesophageal reflux disease and perhaps for eradicating H. pylori infection when a proton pump inhibitor is given with antibiotics. Once-daily dosing in the morning is more effective than dosing in the evening for all proton pump inhibitors with respect to the suppression of intragastric acidity and daytime gastric acid secretion in particular, which may result from a better bio-availability being achieved with the morning dose. When higher doses are needed, these drugs must be given twice daily to achieve the optimal suppression of 24 hour intragastric acidity. Preliminary

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results have shown that esomeprazole, the optical isomer of omeprazole, given at 40 mg, is significantly more effective than omeprazole 40 mg, lansoprazole 30 mg or pantoprazole 40 mg for suppressing gastric acid secretion. However, more studies in different patient populations are needed to compare esomeprazole with the existing proton pump inhibitors with regard to their efficacy, cost-effectiveness and long-term safety for the management of acid-related disorders.

Key words: gastric acid; pepsin; acid suppression; H2-receptor antagonists; proton pump inhibitors; omeprazole; lansoprazole, pantoprazole; rabeprazole; esomeprazole.

Over the past three decades, there have been three important advances in the treatment of acid-related disorders. These include the discovery of H2-receptors and proton pumps for controlling gastric acid secretion, the successful synthesis of H2-receptor antagonists (H2RAs) in the early 1970s and proton pump inhibitors (PPIs) in the 1980s and, more recently, the appreciation of the importance of Helicobacter pylori infection in the pathogenesis of peptic ulcer disease. Although the pharmacological inhibition of gastric acid secretion heals peptic ulcers effectively, recurrence inevitably occurs in virtually all patients after anti-secretory treatment has ceased.

In light of our present understanding, two major forms of peptic ulcer exist: ulcers related to H. pylori infection and ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). In both cases, anti-secretory agents play an important role in the management of peptic ulcer disease. Furthermore, gastro-oesophageal reflux disease (GORD), another increasingly common acid-related disorder, is not associated with either H. pylori infection or NSAID use. Therefore, reducing gastric acid secretion and preventing the acidic gastric contents entering the oesophagus, causing oesophageal mucosal damage and reflux symptoms, comprise the major management strategy for patients with GORD.1

Numerous controlled clinical trials have shown that the healing of acid-related disorders (duodenal and gastric ulcers and erosive oesophagitis) is highly correlated with the degree of gastric acid suppression achieved using anti-secretory agents. A comprehensive analysis of 24 hour intragastric acidity data obtained from patients with peptic ulcer disease has confirmed the hypothesis that the healing of peptic ulcers and the relief of acid-related symptoms are both significantly correlated with three key parameters of acid suppression. These are the degree and duration of acid suppression over the 24 hour period and the length of anti-secretory treatment in weeks.2–5 There is a dynamic relationship between the suppression of gastric acid secretion and the healing of duodenal ulcers, gastric ulcers and erosive oesophagitis. For example, the healing of a duodenal ulcer or erosive oesophagitis can be predicted by the proportion of time (expressed as a percentage of the 24 hour period) that the intragastric pH is above 3 (for a duodenal ulcer) or the intra-oesophageal pH is above 4 throughout the 24 hour period.

Results from numerous comparative clinical trials and meta-analyses of these studies have shown that PPIs are significantly more effective than H2RAs for suppressing gastric acid secretion and healing duodenal and gastric ulcers and erosive oesophagitis, and for the relief of acid-related symptoms. PPIs are also significantly more effective than H2RAs or misoprostol for preventing and healing NSAID-associated ulcer disease.6

This chapter reviews the pharmacological and pharmacodynamic essentials of both H2RAs and PPIs and their clinical relevance in the management of acid-related disorders.
**H₂-receptor antagonists**

Four H₂RAs have been used worldwide for more than two decades—cimetidine, ranitidine, famotidine, and nizatidine—roxatidine also having been marketed in a number of regions. These agents are specific antagonists that inhibit acid secretion by competitively and reversibly blocking the H₂-receptors on the basolateral membrane of the parietal cell. The drugs differ slightly in structure but have many similarities in their pharmacological properties. H₂RAs only partially inhibit the acid secretion stimulated by gastrin and are more effective for inhibiting intragastric acidity during periods of basal acid secretion.⁷,⁸ As the longest period of basal acid secretion occurs nocturnally, dosing after an evening meal or at bedtime is optimal for these agents.⁹,¹⁰

In an early study comparing different dosing regimens of cimetidine (400 mg twice a day or 300 mg at night) and ranitidine (150 mg twice daily or 300 mg at night), Gledhill et al showed no significant difference between these two dosing regimens for both cimetidine and ranitidine in the reduction of 24 hour intragastric acidity. Nocturnal acid secretion was, however, controlled significantly better with ranitidine at night.⁹

Furthermore, recent studies suggest that bedtime ranitidine 150 or 300 mg is more effective than bedtime omeprazole 20 mg for controlling the nocturnal acid breakthrough observed in subjects treated with omeprazole 20 mg twice daily.¹¹,¹² Acid breakthrough, defined as a decrease in intragastric pH to less than 4 for 1 hour or more, occurs nocturnally in more than 90% of subjects receiving omeprazole 20 mg twice daily.¹² This phenomenon is considered to be driven largely by histamine.¹¹,¹² The clinical significance of the nocturnal acid breakthrough is, however, not clear.

Although evening dosing regimens provide prolonged nocturnal acid suppression, they are ineffective for sufficiently increasing daytime intragastric pH and cannot overcome food-stimulated acid secretion.¹³,¹⁴ Many patients do not respond to H₂RAs despite increased dosages.¹⁵ Furthermore, H₂RAs are not effective for suppressing peptic activity and pepsin secretion during the daytime, as shown in many 24 hour pH-monitoring studies.¹⁶–¹⁸ The suppression of nocturnal acid secretion achieved with an evening dose of H₂RAs may therefore be more relevant for managing patients with duodenal ulcer than with GORD, since healing GORD requires the effective control of both daytime and nighttime gastric acid secretion.

Numerous controlled clinical trials have been published regarding the effects of H₂RAs on gastric acid suppression and the relationship between the inhibition of acid secretion and the healing of peptic ulcers and GORD, and these have been systematically analysed by our group.²–⁵,¹⁹ Nevertheless, several interesting and important issues deserve further discussion, for example the development of tolerance to H₂RAs, rebound acid hypersecretion and the pharmacodynamics and clinical uses of low-dose H₂RAs.

**Tolerance**

‘Tolerance’ is a term frequently used in clinical pharmacology but often misunderstood and poorly explained in studies examining the effect of H₂RAs in the treatment of acid-related disorders. By definition, ‘tolerance’ has developed when it becomes necessary to increase the dose of a drug to obtain an effect previously seen with a lower dose. This strict definition does not apply to H₂RAs for several reasons:

1. Increasing the dose of ranitidine does not achieve the same anti-secretory effect in the clinical situation or experimentally when given by a pH feedback pump after chronic oral dosing.²⁰
2. Clinical experience with H$_2$RAs during chronic treatment, for example in the maintenance treatment of duodenal ulcer, does not support progressive pharmacological tolerance since there is no need to increase the dose of H$_2$RAs in order to keep patients in remission.\textsuperscript{21}

Therefore, the change of response to H$_2$RAs may be better explained by an exaggerated ‘first-dose’ effect, as has been shown with many types of anti-hypertensive drugs.\textsuperscript{20}

Theoretically, the development of tolerance to H$_2$RAs is particularly likely to occur when a high dose is used. This has been confirmed by several recent studies examining the anti-secretory effect of high-dose ranitidine given orally over varying periods of continuous treatment.\textsuperscript{22–26} Lachman and Howden examined the development of pharmacological tolerance to 5 day continuous treatment with ranitidine 150 mg four times a day, a recommended dose for treating patients with GORD.\textsuperscript{22} The mean 24 hour intragastric pH increased from 2.62 at pre-dosing to 4.22 on day 1 of ranitidine administration and 3.28 on day 5. There was a significant fall in the mean 24 hour intragastric pH between day 1 and day 5 of ranitidine treatment ($P < 0.001$). Similar differences were also observed in the mean percentage of time that the intragastric pH was above 3, 4 and 5 between day 1 and day 5. However, neither the variation in pharmacokinetic parameters of ranitidine over the 5 days of treatment nor the subjects’ \textit{H. pylori} status could explain the decrease in the anti-secretory effect of ranitidine.\textsuperscript{22}

It seems that pharmacological tolerance develops even more quickly when H$_2$RAs are administered intravenously rather than orally. In a study comparing the effects of intravenous ranitidine and omeprazole for treating patients with bleeding peptic ulcer, Labenz et al found a significant loss of anti-secretory effect for ranitidine (0.25 mg/kg per hour after a bolus of 50 mg) during the second half of a 24 hour treatment when the intragastric pH was below 6 for 20–46\% of the time compared with 0.1–0.15\% with omeprazole (8 mg per hour after a bolus of 80 mg).\textsuperscript{25} Furthermore, an individual dose titration of ranitidine has proved to be ineffective in overcoming the loss of anti-secretory effect once tolerance has been established.\textsuperscript{24} The results of these studies may provide some explanation for the disappointing effect of H$_2$RAs for adequately controlling gastric acid secretion, especially in conditions in which extended anti-secretory treatment is needed.

**Rebound acid hypersecretion**

A temporary increase in gastric acid secretion to above pre-treatment values after the abrupt withdrawal of H$_2$RAs has been reported in many studies in both healthy volunteers\textsuperscript{27–29} and patients with a history of duodenal ulcer.\textsuperscript{30,31} This rebound acid hypersecretion may contribute to a rapid return of ulcer symptoms and ulcer recurrence. Interestingly, rebound is seen more often in subjects treated with cimetidine, ranitidine and nizatidine than in those receiving famotidine, although no direct comparison has been made between H$_2$RAs.\textsuperscript{28,30} There is no difference between \textit{H. pylori}-positive and negative subjects with respect to the degree of rebound acid hypersecretion.\textsuperscript{29}

The underlying mechanism of rebound acid hypersecretion is not clearly understood and cannot be associated with hypergastrinaemia.\textsuperscript{28,31} Recent animal studies have shown that upregulation of the H$_2$-receptor and adenylate cyclase of the parietal cell may be the cause of acid hypersecretion after the withdrawal of prolonged treatment
with H₂RAs. Although the rebound acid hypersecretion is a transient phenomenon, the clinical implications should not be ignored.

**Low-dose H₂RAs**

Low-dose H₂RAs such as ranitidine 75 mg or famotidine 10 mg have been available as over-the-counter medications for a few years and have proved to be effective and safe for self-controlling acid-related symptoms. Results from pharmacodynamic studies have shown that low-dose H₂RAs are significantly more effective for suppressing acid secretion than antacids and placebo even though the onset of action with the low-dose H₂RAs is slower than that seen with antacids.

In a three-way cross-over study comparing the anti-secretory effects of single-dose ranitidine 75 mg with cimetidine 200 mg or placebo in 24 healthy volunteers, Grimley et al found that ranitidine was significantly more effective than cimetidine or placebo for inhibiting intragastric acidity during both the daytime and the night-time periods. The mean weighted intragastric acidity (mmol/l) in the daytime (0–10 hours post-dosing) was 31.03 with placebo, decreasing to 10.37 (P < 0.001 versus placebo) with ranitidine and 16.23 (P < 0.001 versus placebo) with cimetidine. Ranitidine was significantly more effective than cimetidine for controlling intragastric acidity during this period (P < 0.001). During the night (10–20 hours post-dosing), similar differences were observed, except for the comparison between cimetidine and placebo. The results suggest that the acid inhibitory effect achieved with ranitidine 75 mg lasts longer than that with cimetidine 100 mg. The anti-secretory effect of low-dose H₂RAs can, however, be affected when the drugs are taken with food.

It is worth pointing out that most pharmacodynamic data published in the literature have been obtained from healthy volunteers. It is not clear, therefore, whether these data can be translated easily to patients who self-medicate to control acid-related symptoms. More studies are needed to assess the anti-secretory effect of low-dose H₂RAs in the self-medicating population with acid-related symptoms.

**PROTON PUMP INHIBITORS**

The PPIs, omeprazole, lansoprazole, pantoprazole and rabeprazole are potent acid-suppressing agents that inhibit the final common pathway for acid secretion by the parietal cell. They all contain a pyridylmethylsulphinyl benzimidazole moiety but differ from each other as a result of substitutions on the pyridine or benzimidazole rings. The PPIs are all weak bases with a pKₘ of about 4, and they share a generally similar mechanism of action at the parietal cell. As such, they concentrate in the acidic compartment of the secretory canaliculus of the parietal cells and then undergo an acid-catalysed transformation to a tetracyclic cationic sulphenamide. The sulphenamide reacts with specific cysteines, which results in the inhibition of the H⁺, K⁺-ATPase proton pumps. The binding is covalent with omeprazole, lansoprazole and pantoprazole, the inhibition of the activity of the acid pump being essentially irreversible, so the suppression of acid secretion is more complete than with other classes of anti-secretory drug. The substituted benzimidazoles, however, bind only to those pumps which are inserted into the secretory canalicular membrane and actively secreting acid, sparing those inactive pumps which are resting in the cytosol.

The inhibition of the secreting pumps results in an initially profound but time-dependent elevation of intragastric pH. The recovery of acid secretion depends largely
on the rate of de novo synthesis of acid pumps and the breakdown of the covalent complex. When the drug concentration, after the first dose, has decreased to below threshold, any pumps that become inserted into the secretory canaliculus are able to secrete acid until the second dose. Newly active pumps are inhibited by the second dose, which also has a cumulative effect on the pre-existing pumps, although this cumulative inhibition of acid secretion will eventually be balanced out by newly synthesized pumps. Therefore, intragastric acidity is rapidly restored after a single oral dose of PPI.

Twenty-four hour gastric anacidity does not occur with the once or even twice-daily oral administration of PPIs. In order to achieve anacidity, the continuous intravenous administration of a PPI may be needed. The full restoration of acid secretion, as measured by 24 hour intragastric pH, generally occurs 72 hours after the last dose of a PPI. Therefore, acid inhibition achieved by the PPIs targeting the proton pump is more effective than that achieved by agents targeting the parietal cell receptors.

PPIs have been shown in numerous clinical trials to be significantly better than any H₂RA for suppressing intragastric acidity. PPIs result in a prolonged and highly effective inhibition of both basal and stimulated gastric acid secretion to all known stimuli, including meals. The effect of PPIs on intragastric acidity is highly dose dependent, the rapidity of onset of action depending on the bio-availability of the individual PPI.

The PPIs also have effect on peptic activity, decreasing pepsin output and reducing secretory volume, which directly inhibits peptic activity, whereas increasing the intragastric pH to a level greater than 4 indirectly eliminates peptic activity because the activation of pepsin is highly pH dependent. This mechanism may partly explain the difference between PPIs and H₂RAs in healing peptic ulcer and especially erosive oesophagitis, because the intragastric pH achieved with H₂RAs over a 24 hour period mostly still allows pepsin to show some proteolytic activity, leading to the retardation of mucosal healing.

Omeprazole

Omeprazole was the first of the PPIs shown to be superior to H₂RAs in suppressing gastric acid secretion, relieving symptoms and healing gastric and duodenal ulcers and GORD. Meta-analyses of clinical trials have shown a clear advantage for omeprazole over various dose regimens of H₂RAs for the inhibition of 24 hour intragastric acidity and the healing of peptic ulcers and GORD. Omeprazole 20 mg in the morning suppresses 90% of 24 hour intragastric acidity, 88% of nocturnal acidity and 92% of daytime acidity, whereas the best acid suppression profile achieved with H₂RAs occurs with ranitidine 300 mg at bedtime, which inhibits 24 hour intragastric acidity by 68%, nocturnal acidity by 90% and daytime acidity by 50%.

Although the reduction of nocturnal intragastric acidity is an important determinant of ulcer healing, the suppression of 24 hour intragastric acidity has proved to be more critical, especially for the management of patients with GORD. If, for example, the suppression of nocturnal acidity is increased from 24 to 95% by an H₂RA, a therapeutic gain of 21% in duodenal ulcer healing can be expected at 4 weeks. However, when the suppression of overall 24 hour acidity is increased from 40 to 100% by the inclusion of the PPI effect, the therapeutic gain is almost doubled, to 40%.

Omeprazole inhibits basal and maximum acid secretion stimulated by all known stimuli and in a dose-dependent manner, although there are marked variations in individual responses to omeprazole at lower doses of 5–10 mg. In an early report,
Howden et al studied the effects of single and repeated doses of omeprazole 10 mg on gastric acid secretion in six healthy volunteers. Analyses of gastric acid secretion were performed on the first and seventh days of treatment, the results being compared with those obtained from a previous placebo study. After single doses of omeprazole, no significant changes in basal acid output (BAO) or pentagastrin-stimulated peak acid output (PAO) were seen compared with the results achieved with placebo. After 7 days treatment, however, there was a significant reduction in both BAO (93.1%) and PAO (66.5%). Pharmacokinetic studies confirmed a significant increase in the bio-availability of omeprazole after repeated dosing since the \( C_{\text{max}} \) increased significantly in all subjects from 92 \( \mu g/l \) per hour on the first day to 193 \( \mu g/l \) per hour on the seventh day and so did the area under the plasma omeprazole concentration time curve from 218 \( \mu g/l \) per hour to 339 \( \mu g/l \) per hour.

Higher doses of omeprazole (20–80 mg daily) provide a much more predictable inhibition of 24 hour intragastric acidity. Omeprazole 40 mg given in the morning and in the evening increased the median 24 hour intragastric pH to 5.0 and 4.5, compared with 1.9 with placebo, after 5 days of treatment in eight healthy volunteers in a cross-over study. This is equivalent to an inhibition of hydrogen ion activity of over 99% for both omeprazole regimens.

The increase in the anti-secretory effect of omeprazole was caused by the increased absorption of the drug as measured by the \( C_{\text{max}} \) and area under the curve (AUC). This enhanced drug absorption may, in part, result from the pharmacological characteristics of omeprazole as an acid-labile compound such that its absorption increases as intragastric acidity decreases. Indeed, as reported in many other studies, the bio-availability of omeprazole increases with the duration of treatment. In healthy volunteers, the bio-availability of enteric-coated omeprazole 20 mg was 40% on the first day, increasing to 65% on the seventh day of dosing.

Unlike the situation with \( H_2 \)-RAs, the morning administration of omeprazole is better than evening dosing for suppressing 24 hour intragastric acidity. Chiverton et al found that, in patients with a healed duodenal ulcer, omeprazole 20 mg given in the morning was significantly better than dosing in the evening for inhibiting gastric acid secretion. The mean 24 hour intragastric pH was 3.9 \( \pm \) 1.8 for dosing in the morning, 2.9 \( \pm \) 1.1 for the evening dose and 1.7 \( \pm \) 0.1 for placebo (\( P < 0.01 \) between the morning dose and placebo).

The profound suppression of 24 hour intragastric acidity also has an important impact on peptic activity. By plotting the frequency distribution of 24 hour intragastric pH against the peptic activity curve, Hirschowitz et al demonstrated that the majority of pH values achieved during treatment with cimetidine 1 g and ranitidine 300 mg daily were below 3 and within the range of maximum peptic activity, whereas omeprazole 30 mg daily consistently increased the intragastric pH to above 4, a level at which peptic activity is essentially abolished. This additional advantage of omeprazole over \( H_2 \)-RAs may be particularly relevant to healing both peptic ulcers and especially erosive oesophagitis.

### Lansoprazole

Lansoprazole was the second PPI approved for treating patients with acid-related disorders. In approved therapeutic doses, lansoprazole, given orally, has a higher bio-availability and faster onset of anti-secretory effect than omeprazole, although both agents have many similarities in structure and mechanism of action. Results from pharmacokinetic studies have shown that, after a single dose of lansoprazole, the
absolute bio-availability is 81% for the 15 mg and 85–91% for the 30 mg doses respectively and remains steady after repeated dosing. The fast onset of action with lansoprazole has been confirmed in a recent study in nine healthy volunteers, in whom once-daily lansoprazole 30 mg was given for 4 days, the maximum anti-secretory effect being obtained 6 hours after the first dose and remaining consistent with subsequent dosing.

Pharmacodynamic studies have shown that lansoprazole inhibits basal and stimulated gastric acid secretion dose-dependently. In an early study of the effect of different doses of lansoprazole (15, 30 and 60 mg given for 1 week) on BAO and gastrin-stimulated maximum acid output (MAO), Müller et al found a significant and dose-dependent decrease in BAO and MAO in all subjects. On days 2 and 8, a significant decrease in MAO was seen with all three doses of lansoprazole, the reduction in MAO observed on day 8 being more pronounced compared with the pre-treatment MAO (a fall of 94% for the 60 mg, 90% for the 30 mg and 69% for the 15 mg dose of lansoprazole respectively). Together with the decrease in MAO, the volume of gastric secretion was also significantly reduced. All these changes returned to normal 1 week after stopping the treatment, suggesting the end of inhibition of acid secretion by lansoprazole.

In patients with healed duodenal ulcer and acid hypersecretion, lansoprazole also inhibited dose-dependently and significantly the BAO and pentagastrin-stimulated PAO. All three doses of lansoprazole (10, 20 and 30 mg administered as a single dose in the evening) significantly inhibited the PAO after the first dose on day 1 and repeated doses on day 7. It seems, however, that lansoprazole at a dose of 10 mg did not sufficiently inhibit the BAO even after repeated dosing for 7 days, whereas the BAO was effectively suppressed by doses of 20 and 30 mg but only on day 7. The less effective anti-secretory effect reported in this study might have resulted from the different dosing schedule used in this study because the rate of absorption and bioavailability of lansoprazole have been shown to be lower when the dose is administered in the evening than with dosing in the morning.

Lansoprazole 30 mg given twice daily has proved to be the maximum dose frequency to achieve the optimal anti-secretory effect compared with other dose frequencies. Doses greater than 30 mg twice daily generally do not show any significant advantages over lansoprazole 30 mg twice daily in suppressing intragastric acidity. In a comparative study of multiple doses of lansoprazole (30 mg once daily, 30 mg twice daily, 45 mg twice daily and 60 mg twice a day) and omeprazole 20 mg twice a day, Timmer et al have shown that lansoprazole 30 mg twice daily has the best anti-secretory profile in terms of the holding time that the intragastric pH was above 5, which has been suggested as an optimal intragastric pH for combination with antibiotics in the eradication of H. pylori infection.

Several comparative studies have indicated that a single dose of lansoprazole 30 mg has a better effect than omeprazole 20 mg in suppressing intragastric acidity because of the pharmacokinetic differences between the two PPIs. After the first dose, the bio-availability of lansoprazole is over 85% and remains constant after repeated dosing, whereas the bio-availability of omeprazole is only 35% after the first dose and rises to about 60% after repeated dosing. The plasma half-life of lansoprazole is also longer and the t_max significantly shorter, hence lansoprazole 30 mg has a faster onset of action than omeprazole 20 mg, providing a maximum anti-secretory effect on day 1.

Results from a comparative study have shown that, when compared with placebo, lansoprazole 30 mg per day decreased meal-stimulated acid secretion over a 24-hour period on the first day by 45.1%, followed by omeprazole 40 mg per day by 41.7%.
lansoprazole 15 mg per day by 34.6%, and omeprazole 20 mg per day by 15.6%. When compared with the new tablet formulation of omeprazole 20 mg, lansoprazole 30 mg has also been shown to be more effective for suppressing intragastric acidity, with a lower individual variability.

Therefore, according to pharmacodynamic studies, there is a dose-dependent effect for lansoprazole and omeprazole on the suppression of intragastric acidity with a potency order of lansoprazole 60 mg > lansoprazole 30 mg ≈ omeprazole 40 mg > omeprazole 20 mg ≈ lansoprazole 15 mg. The difference in acid suppression between PPIs may be of clinical importance since the relief of acid-related symptoms as well as the healing of gastric and duodenal ulcers and erosive oesophagitis correlates with the degree of suppression of intragastric acidity.

**Pantoprazole**

Like omeprazole and lansoprazole, pantoprazole binds covalently to the H\(^+\), K\(^+\)-ATPase and irreversibly inhibits acid secretion by the proton pump. Although it shares many similarities in terms of structure and mechanism of action with the former two PPIs, pantoprazole is chemically more stable than omeprazole or lansoprazole under near-neutral conditions. This greater acid stability may improve the tissue selectivity of the drug for the parietal cell since it reduces the likelihood of the compound reacting with proteins containing thiol groups that lie outside the parietal cell. After a single oral dose, pantoprazole 40 mg is absorbed rapidly, with an average t\(_{\text{max}}\) of about 2.5 hours, this being slightly longer than the t\(_{\text{max}}\) achieved with omeprazole (1–3 hours) and lansoprazole (2 hours). The absolute bio-availability of pantoprazole has been reported to be 75–80%, this increasing with repeated dosing. Pantoprazole also shows dose linearity and thus a predictable anti-secretory effect.

Pantoprazole 20–60 mg once daily given orally produces a dose-dependent inhibition of 24-hour intragastric acidity in both healthy volunteers and patients with peptic ulcer disease, with minimal additional anti-secretory effects at doses above 60 mg. Hannan et al. studied the anti-secretory effects of pantoprazole 40 mg and 60 mg given for 5 days and found that, on day 5, the median 24 hour intragastric pH values differed significantly between placebo (pH 1.4), pantoprazole 40 mg (pH 2.3) and pantoprazole 60 mg (pH 3.5). The holding time for the intragastric pH above 3 was also significantly longer with pantoprazole 40 mg (33%) and 60 mg (58%) compared with placebo (14.9%). This was equivalent to a decrease in 24 hour intragastric acidity of 87% with 40 mg and 99% with 60 mg pantoprazole respectively.

However, in a more recent study reported by Koop et al., pantoprazole 40, 80 and 120 mg was found to be equally effective for inhibiting gastric acid secretion. In a review of the pantoprazole literature, Fitton and Wiseman found that the median 24 hour intragastric pH achieved with repeated dosing of pantoprazole 40 mg was 2.3–4.3, suggesting a considerable variation in the anti-secretory effect of pantoprazole after the oral administration of the 40 mg dose.

Like the former two PPIs, pantoprazole given in the morning is significantly better than dosing in the evening. This difference is, however, caused largely by a greater suppression of daytime gastric acid secretion obtained with the morning dose than with dosing in the evening.

In comparison to H\(_2\)RAs, pantoprazole 40 mg was significantly superior to ranitidine 300 mg once daily in terms of the inhibition of median 24 hour intragastric pH (4.2 versus 2.7) and daytime pH (4.4 versus 2.0) in healthy volunteers. In patients with grade II–III oesophagitis, pantoprazole 40 mg was significantly more effective than
ranitidine 150 mg twice daily for increasing the median intragastric pH and maintaining a longer holding time with the intragastric pH above 4, although there was no significant difference in the healing of the oesophagitis, probably because of the small number of patients studied.\textsuperscript{79} When compared with omeprazole 20 mg and lansoprazole 30 mg, pantoprazole 40 mg was as effective or better than omeprazole 20 mg for suppressing gastric acid secretion, but no better than lansoprazole 30 mg on the first day of dosing as a result of its relatively slower onset of action.\textsuperscript{53,80}

**Rabeprazole**

Rabeprazole is the fourth PPI that has been approved for treating acid-related disorders. Although rabeprazole was designed to be more potent than omeprazole in suppressing gastric acid secretion, it appears to dissociate more quickly and completely from the $\text{H}^+\text{-K}^+$-ATPase than does omeprazole or lansoprazole, suggesting a partially reversible inhibition of the proton pump.\textsuperscript{81}

In animal studies in vitro, rabeprazole was more potent than omeprazole for inhibiting the proton pump, but the duration of inhibition was considerably shorter than that seen with omeprazole\textsuperscript{82} and lansoprazole because of the rapid dissociation from the proton pump.\textsuperscript{83} In healthy volunteers, after single oral doses of rabeprazole of 1–80 mg, the maximum plasma concentration and AUC values increased with increasing doses, but the $t_{\text{max}}$ and plasma half-life were not dose dependent.\textsuperscript{84} After a single dose of rabeprazole 20 mg, the $C_{\text{max}}$ was 0.406 mg/l, the $t_{\text{max}}$ 3.1 hours, the AUC 0.809 mg/l and the plasma half-life 1.02 hours in healthy volunteers.\textsuperscript{84}

The anti-secretory effect of rabeprazole has been examined in several randomized, placebo-controlled, cross-over studies.\textsuperscript{85–87} In a 7 day study of the effect of different doses of rabeprazole on 24 hour intragastric acidity, Blanshard et al found that, on day 7, dosing with rabeprazole 10, 20 and 40 mg significantly decreased the 24-hour intragastric acidity when compared with placebo. No significant difference in acid suppression was shown between the three doses of rabeprazole.\textsuperscript{85}

In another dose-ranging study involving 38 H. pylori-infected asymptomatic volunteers, rabeprazole at a dose of 5, 10, 20 or 40 mg once daily, or placebo, was given orally for 7 days.\textsuperscript{86} The 24 hour intragastric acidity was monitored, as was the peptone meal-stimulated acid output. The authors found that the BAO and the meal-stimulated acid output were significantly and dose-dependently suppressed by rabeprazole compared with placebo on days 1 and 7, the inhibition being most pronounced on day 7. They also found that the half-time for the recovery of acid secretion was about 48 hours with the 5 mg dose and longer for the higher doses of rabeprazole.\textsuperscript{86}

In patients with reflux oesophagitis, rabeprazole has been shown to be effective for normalizing acid reflux time over the 24 hours that the oesophageal pH was below 4, with an increasing effect over the duration of treatment.\textsuperscript{88} The 24 hour intragastric pH increased with rabeprazole 20 mg from 1.86 at base line to 3.71 on day 1 and 4.17 on day 7. With rabeprazole 40 mg, the intragastric pH increased from 2.01 to 4.37 on day 1 and 4.65 on day 7.\textsuperscript{88} There is currently only one published study comparing the anti-secretory effect of rabeprazole against that of omeprazole and placebo in healthy volunteers.\textsuperscript{89} The results show that rabeprazole 20 mg given orally in the morning has a faster onset of anti-secretory activity than omeprazole 20 mg and produces a significantly greater decrease in 24 hour intragastric acidity after a single dose of medication (406 mmol/l per hour on day 1 with rabeprazole versus 660 mmol/l per hour with omeprazole, $P < 0.001$).\textsuperscript{89}
Esomeprazole

Esomeprazole, the first optical isomer of omeprazole, has recently been approved in Europe for treating acid-related disorders. Preliminary results suggest that esomeprazole 20 or 40 mg per day achieves a significantly higher healing rate of erosive oesophagitis and provides faster symptom relief in patients with GORD than does omeprazole 20 mg per day.90

Although esomeprazole was designed differently from the existing PPIs and has a different pharmacokinetic profile, it, like omeprazole, acts by inhibiting the H⁺, K⁺-ATPase, the final pathway of gastric acid secretion by the parietal cell. Preliminary results from several pharmacodynamic studies have shown that, on a dose-by-dose basis, the oral administration of esomeprazole is significantly more effective than that of omeprazole, lansoprazole and pantoprazole for controlling intragastric acidity in patients with GORD.91–93

Lind et al reported a cross-over study comparing the anti-secretory effects of esomeprazole 20 mg and 40 mg with omeprazole 20 mg once daily given for 5 days in 36 patients with GORD.94 Esomeprazole 20 mg and 40 mg effectively maintained the intragastric pH at above 4 for a mean of 12.7 and 16.8 hours over the 24 hour period respectively, compared with 10.5 hours with omeprazole 20 mg. The median 24 hour intragastric pH achieved with esomeprazole 20 mg (pH = 4.1) and 40 mg (pH = 4.9) were also significantly higher than that seen with omeprazole 20 mg (pH = 3.6). Furthermore, the inter-patient variability in intragastric pH and AUC was consistently less with esomeprazole than with omeprazole. The significantly improved pharmacodynamics of esomeprazole over the existing PPIs offers great potential for the better management of acid-related disorders, although more studies are needed to assess the effect of esomeprazole in different patient populations, its cost-effectiveness and its long-term safety.

SUMMARY AND CONCLUSION

Although eradicating H. pylori infection heals the majority of peptic ulcers, the pharmacological reduction of gastric acid secretion plays an important role in the management of acid-related disorders including ulcers associated with H. pylori infection and NSAID use, or non-H. pylori, non-NSAID ulcers or GORD. There is a dynamic relationship between the suppression of intragastric acidity and the healing of peptic ulcers and erosive oesophagitis. However, the suppression of intragastric acidity achieved with H₂RAs has proved to be suboptimal for effectively controlling acid-related disorders. Furthermore, the rapid development of tolerance to H₂RAs and the rebound acid hypersecretion seen following the withdrawal of an H₂RA further limit their clinical application.

PPIs effectively inhibit gastric acid secretion stimulated by all known stimuli and are more potent anti-secretory agents than H₂RAs, as shown by numerous comparative, controlled clinical trials. Four PPIs are currently available, all of which have been proved to be very effective for suppressing intragastric acidity, even though variations exist in their rapidity of onset of action and the potency of acid inhibition after oral administration at the approved therapeutic doses, which may have important clinical implications for the treatment of GORD. Once-daily dosing in the morning is more effective than dosing in the evening for all PPIs with respect to the suppression of intragastric acidity and daytime gastric acid secretion in particular, which may be due
to a better bio-availability achieved with morning dosing. When higher doses are needed, these drugs must be given twice daily to achieve an optimal suppression of 24 hour intragastric acidity.

Esomeprazole is a new PPI with an improved pharmacodynamic profile over the existing PPIs. Preliminary results from comparative trials have shown its clear superiority over the existing PPIs in suppressing intragastric acidity and healing

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**Practice points**

- gastric acid suppression achieved with H₂RAs is suboptimal for managing acid-related disorders, especially GORD
- an evening dose of H₂RAs is more effective than a daily dose for controlling nocturnal acid secretion
- a rapid development of tolerance to H₂RAs occurs and cannot be overcome by dose adjustment
- rebound acid hypersecretion is common with all H₂RAs after stopping medication
- low-dose H₂RAs are significantly more effective than placebo and antacids for controlling intragastric acidity
- PPIs are significantly more effective than H₂RAs for suppressing gastric acid secretion
- the healing of peptic ulcer and GORD and the relief of acid-related symptoms are significantly correlated to the degree and duration of acid suppression over the 24 hour period and the length of anti-secretory treatment in weeks
- differences in bio-availability and pharmacodynamics exist between the PPIs at the recommended doses, and these may have clinical implications
- on a dose-by-dose basis, esomeprazole is significantly more effective than the existing PPIs for inhibiting intragastric acidity
- PPIs are significantly more effective given in the morning than in the evening for suppressing 24 hour intragastric acidity
- twice-daily dosing is recommended if a high-dose PPI is required

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**Research agenda**

- the anti-secretory effects of low-dose H₂RAs need to be evaluated in self-medicating populations
- whether tolerance and rebound acid hypersecretion develop with low-dose H₂RAs needs to be addressed
- an updated analysis of the relationship between the suppression of intragastric acidity and the healing of GORD is needed, involving all the PPIs
- pharmacological and pharmacodynamic studies are needed to evaluate the anti-secretory effect of PPIs in non-\textit{H. pylori}-non-NSAID-associated peptic ulcer disease because this type of peptic ulcer appears to be more common than was previously thought
- the efficacy, cost-effectiveness and long-term safety of esomeprazole need to be evaluated in different patient populations and compared with those of the existing PPIs
GORD. More studies are, however, needed to assess its efficacy in different patient populations, its cost-effectiveness and, in particular, its long-term safety in comparison with the existing PPIs.

REFERENCES


