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# Pharmacological and pharmacodynamic essentials of $H_2$-receptor antagonists and proton pump inhibitors for the practising physician

Jia-Qing Huang MD, MSc
Medical Research Scientist

Richard H. Hunt* MD, FRCP, FRCP(Ed), FRCPC, FACG
Professor of Medicine

*Division of Gastroenterology, Department of Medicine, McMaster University Medical Center, Hamilton, Ontario, Canada*

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 $H_2$-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. $H_2$-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 $H_2$-receptor antagonists and the rebound acid hypersecretion after the withdrawal of an $H_2$-receptor antagonist further limit their clinical use. Although low-dose $H_2$-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

*Corresponding author.

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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; $H_2$-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 $H_2$-receptors and proton pumps for controlling gastric acid secretion, the successful synthesis of $H_2$-receptor antagonists ($H_2$RAs) 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 $H_2$RAs 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 $H_2$RAs or misoprostol for preventing and healing NSAID-associated ulcer disease.[6]

This chapter reviews the pharmacological and pharmacodynamic essentials of both $H_2$RAs and PPIs and their clinical relevance in the management of acid-related disorders.

## $H_2$-RECEPTOR ANTAGONISTS

Four $H_2$RAs 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 $H_2$-receptors on the basolateral membrane of the parietal cell. The drugs differ slightly in structure but have many similarities in their pharmacological properties. $H_2$RAs 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 $H_2$RAs despite increased dosages.[15] Furthermore, $H_2$RAs 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 $H_2$RAs 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 night-time gastric acid secretion.

Numerous controlled clinical trials have been published regarding the effects of $H_2$RAs 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 $H_2$RAs, rebound acid hypersecretion and the pharmacodynamics and clinical uses of low-dose $H_2$RAs.

### Tolerance

'Tolerance' is a term frequently used in clinical pharmacology but often misunderstood and poorly explained in studies examining the effect of $H_2$RAs 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 $H_2$RAs 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.[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.[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.[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.[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' *H. pylori* status could explain the decrease in the anti-secretory effect of ranitidine.[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).[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.[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[27–29] and patients with a history of duodenal ulcer.[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.[28,30] There is no difference between *H. pylori*-positive and negative subjects with respect to the degree of rebound acid hypersecretion.[29]

The underlying mechanism of rebound acid hypersecretion is not clearly understood and cannot be associated with hypergastrinaemia.[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 $H_2$RAs.[32] Although the rebound acid hypersecretion is a transient phenomenon, the clinical implications should not be ignored.

### Low-dose $H_2$RAs

Low-dose $H_2$RAs 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.[33,34] Results from pharmacodynamic studies have shown that low-dose $H_2$RAs are significantly more effective for suppressing acid secretion than antacids and placebo even though the onset of action with the low-dose $H_2$RAs is slower than that seen with antacids.[35–39]

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.[35] 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 $H_2$RAs can, however, be affected when the drugs are taken with food.[40]

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 $H_2$RAs 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 $pK_a$ 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.[41,42] 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.[43]

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

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