Combined use of proton pump inhibitors and histamine-H₂ receptor antagonists for GERD: What is the rationale?

Gastroesophageal reflux disease (GERD) is a common ailment that ranges in severity from mild to severe. It is defined as any symptom, or damage to the esophageal mucosa, that results from gastric acid reflux into the esophagus. The most common symptom is heartburn, but the condition may lead to esophagitis, stricture, aspiration and Barrett’s esophagus.

Management of Uncomplicated GERD

The most common agents prescribed for the treatment of moderate to severe heartburn are histamine-H₂ receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs). A stepwise approach has been widely used in the management of patients with GERD. It begins with simple treatments, such as antacids or over-the-counter H₂RAs for mild symptoms, and steps up to high dose H₂RAs or PPIs, for more severe symptoms. Lifestyle changes have not been studied extensively; however, patient counseling and implementation of non-pharmacological measures are integral to the treatment of all stages of GERD.

H₂RAs were historically the mainstay of therapy for GERD, particularly for the symptomatic treatment of heartburn. More recently, PPIs have assumed a more prominent role due to their potent and long-term suppression of acid release and superior efficacy in healing documented esophagitis. A meta-analysis of randomized controlled trials evaluated the healing rates and the degree of symptom relief provided by H₂RAs and PPIs in patients with GERD and moderate to severe esophagitis (Grade II to IV). The overall healing proportion was greatest with PPIs (83.6%) compared with H₂RAs (51.9%), sucralfate (39.2%) or placebo (28.2%). The proportion of patients who were heartburn-free was highest with PPIs (77.4%) compared with H₂RAs (47.6%). Overall, PPIs showed faster healing rates and more complete heartburn relief. The studies included in this meta-analysis were restricted to those that assessed acute healing of esophagitis rather than maintenance therapy for recurrence. Various PPIs have been approved in Canada for the initial therapy of patients with more severe GERD symptoms, those with endoscopically documented esophagitis, or those who have not responded to four to eight weeks of H₂RA therapy (Table 1).

Nocturnal Acid Breakthrough

Although the development of more potent and effective acid suppressing agents has greatly reduced the clinical symptoms of GERD, some patients continue to experience symptomatic nocturnal acid breakthrough (NAB) despite treatment with multiple daily doses of PPIs. It is estimated that up to 75% of patients with GERD who are taking PPIs experience NAB. This problem is particularly of concern in patients who require aggressive acid suppression, such as those with Barrett’s esophagus or severe GERD.

NAB, defined as an intragastric pH of >4 when measured with an intragastric probe for ≥1 hour during PPI therapy, has been documented in 70 to 75% of healthy volunteers and patients with GERD. This phenomenon was studied by Peghini and colleagues in patients with GERD, and normal volunteers who received twice daily omeprazole or lansoprazole. Seventy-three percent of all subjects developed NAB within 12 (median 7.5) hours of their evening PPI dose as diagnosed by 24-hour pH recordings. Retrospective studies have consistently reported that greater than 70% of patients treated with PPIs experience NAB. Acid breakthrough occurs about six to seven hours after the evening dose of a PPI, usually between 1:00 and 4:00 AM. NAB was observed at a similar frequency in all patients; however, it is of particular clinical importance in patients with Barrett’s esophagus, severe esophagitis or scleroderma. Common characteristics of patients who experience reflux during NAB include decreased lower esophageal sphincter pressure and ineffective esophageal motility.

Mechanism of Gastric Acid Secretion and PPIs

Gastric acid secretion occurs in response to the endogenous secretion of histamine, gastrin, and acetylcholine. These substances bind to specific receptors on parietal cells and stimulate acid secretion. The final step in the acid secretory pathway is the H⁺/K⁺ ATPase
enzyme (proton pump), which exchanges potassium for hydrogen ions. In GERD, H⁺ secretion is increased due to overactivity of the proton pump. PPIs bind irreversibly to, and thereby inactivate, this enzyme.⁵,⁶

Despite their potent antisecretory properties, PPIs are unable to completely eliminate gastric acidity. Active proton pumps are stimulated by meals and the proportion of active pumps inhibited determines the efficacy of PPIs. There is speculation that new proton pumps are activated during the night by histamine and/or acetylcholine after metabolic elimination of the PPI. Another proposed mechanism for NAB is a possible circadian rhythm in acid secretion, with peak acid secretion occurring at night.⁵⁻⁸

**Treatment of NAB**

Optimization of antisecretory therapy is required in order to eliminate NAB. This approach has led to the use of twice daily PPI therapy in combination with an H₂RA. In *in vitro* data suggests that concomitant use of H₂RAs and PPIs decreases the effectiveness of the latter since their action is dependent upon an acidic environment.⁵⁻⁸ In *in vivo* studies investigating this theory are presented herein.

A few studies have examined the effect of combining twice daily PPI regimens with H₂RAs. The first of these was a double-blind, placebo-controlled, crossover study designed to examine the effect of a twice daily PPI, twice daily PPI plus bedtime omeprazole or twice daily PPI plus a bedtime H₂RA on nocturnal intragastric pH.⁷ Twelve healthy asymptomatic volunteers were pretreated with omeprazole 20 mg twice daily 15 to 30 minutes before breakfast and dinner for seven days. Bedtime placebo or ranitidine was given in a random sequence with a 48-hour washout period. Bedtime omeprazole was given last to avoid a carryover effect. Intragastric pH data were analyzed from the time of intake of the study drug at 10:30 PM until 6:30 AM the next day. Intragastric pH was <4 for 48% of the overnight period with bedtime placebo. The acid breakthrough period was decreased to 31% with bedtime omeprazole (p<0.005 vs placebo), and 5 and 6% with ranitidine 150 mg and 300 mg, respectively (p<0.001 vs placebo; p<0.01 vs omeprazole).

Eleven, seven, four and three of the 12 subjects experienced NAB (pH <4 for >60 min) on 20 mg omeprazole twice daily with bedtime placebo, omeprazole 20 mg (58%, p=NS vs placebo), ranitidine 150 mg (33%, p<0.05 vs placebo) and 300 mg (25%, p<0.05 vs placebo), respectively.

A retrospective study assessed the effects of PPIs given twice daily for seven days, both with and without H₂RAs, on intragastric pH and the occurrence of NAB in GERD patients.¹⁰ Ambulatory pH recordings of three groups of patients were reviewed. Group A patients (n=60) had taken either omeprazole 20 mg or lansoprazole 30 mg twice daily. Group B patients (n=45) had taken omeprazole 20 mg or lansoprazole 30 mg twice daily plus an H₂RA at bedtime (i.e., ranitidine 300 mg, famotidine 40 mg or nizatidine 30 mg). Eleven patients (Group C) had ranitidine added to failing PPI therapy so data were available for both regimens. The median percentage of time that the overnight intragastric pH was >4 was lower in group A than in group B (51% vs 96%, p<0.0001). The median percentage of time that the overnight intragastric pH was >4 increased from 54.6% without an H₂RA to 96.5% after adding a bedtime dose of an H₂RA (p=0.0013) in group C. The mean duration of esophageal acid exposure during NAB was shorter in group B than in group A (18 vs 42 minutes, p=0.04).¹⁰

Another study determined if a bedtime dose of an H₂RA was sufficient to eliminate the requirement for the second daily dose of a PPI.¹¹ This trial was a randomized, double-blind, crossover study in which 20 healthy volunteers received either omeprazole 20 mg twice daily and placebo at bedtime, or omeprazole 20 mg in the morning and ranitidine 150 mg at bedtime for seven days. A one-week washout between study periods was used. Omeprazole 20 mg twice daily was more effective for NAB than substituting ranitidine for the second omeprazole dose. The median percent time recumbent pH was <4 was lower in patients receiving omeprazole 20 mg

---

**Table 1. Recommended once daily dosages of PPIs for GERD and reflux esophagitis**¹³,¹⁴

<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptomatic GERD without esophagitis</th>
<th>Reflux esophagitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial dose</td>
<td>Maintenance dose</td>
</tr>
<tr>
<td>Esomeprazole  (Nexium )</td>
<td>20 mg/day x 2-4 weeks</td>
<td>40 mg/day x 4-8 weeks</td>
</tr>
<tr>
<td>Lansoprazole  (Prevacid )</td>
<td>15 mg/day x 4-8 weeks</td>
<td>30 mg/day x 4-8 weeks</td>
</tr>
<tr>
<td>Omeprazole    (Losec )</td>
<td>10-20 mg/day</td>
<td>20-40 mg/day x 4-8 weeks</td>
</tr>
<tr>
<td>Pantoprazole  (Pantaloc )</td>
<td>40 mg/day x 4 weeks</td>
<td>40 mg/day x 4-8 weeks</td>
</tr>
<tr>
<td>Rabeprazole   (Pariet )</td>
<td>20 mg/day x 4-8 weeks</td>
<td>20 mg/day</td>
</tr>
</tbody>
</table>

* May be increased to 20 or 40 mg/day in the case of recurrence
twice daily compared with patients receiving omeprazole 20mg once daily in the morning and ranitidine 150 mg at bedtime (23.5 vs 44.8%, p=0.02). Sixty percent of patients on omeprazole twice daily had NAB compared to 75% of patients on omeprazole and ranitidine (p=NS).

More recently, a prospective study addressed the chronic effect of H2RAs on NAB. Gastric acidity was monitored during combination treatment (omeprazole 20 mg twice daily plus ranitidine 300 mg at bedtime) for up to one month in 23 healthy volunteers and 20 patients with GERD. Gastroesophageal pH testing was conducted in all participants at baseline (after two weeks of treatment with omeprazole 20 mg twice daily), after one day, one week and four weeks of the addition of ranitidine to PPI therapy. The results showed a significant reduction in gastric acidity after one day of combination treatment; however, there were no statistically significant differences in the percentage of time gastric pH was <4 when comparing the efficacy of two weeks of PPI twice daily alone with one week or one month of PPI plus bedtime H2RA therapy. The clinical significance of these findings is difficult to elucidate since symptoms were not reported. The results indicate that in the majority of patients, addition of bedtime H2RA does little to affect the long-term management of NAB due to the rapid development of tolerance to the H2RA. The authors suggested that intermittent use of combination therapy after exposure to a refluxogenic situation (e.g., after eating a large fatty meal or drinking cocktails) may be most effective for many patients.

Discussion

The majority of patients with GERD are clinically managed with one daily dose of a PPI as recommended in the respective drug monographs. In a subset of patients, however, the unofficial use of twice daily dosing may be required for optimal control. Furthermore, small clinical trials suggest that some patients may benefit from a bedtime dose of an H2RA in addition to twice daily PPI therapy. These include those who do not obtain relief with a twice daily PPI regimen and those with severe esophagitis, Barrett’s esophagus, or extra-esophageal disease, in whom tight control of acid secretion is required.

The trials presented above have several limitations. The major limitation is that the studies measured intragastric pH rather than clinical outcomes, such as worsening symptoms or endoscopic lesions. The clinical importance of NAB in severe esophagitis and Barrett’s esophagus is empirical and requires further study. There are currently no clinical data to support the notion that aggressive acid suppression in these patients impacts the progression or regression of esophagitis. The second limitation is that few studies evaluated GERD patients prospectively; therefore, there is a lack of data from well-designed studies to support the evidence-based use of a bedtime dose of an H2RA and any proposed use is purely empirical. More clinical evidence is required to assess the development of tolerance to H2RAs in the setting of NAB; some data suggests that intermittent rather than prolonged use of combination therapy may be more effective. For patients who are experiencing inadequate control of NAB on a twice daily PPI, the addition of an H2RA to twice daily PPI therapy may be more cost-effective than adding a third bedtime dose of a PPI.

ACKNOWLEDGMENT

Denis Belanger, Yasmin Khalig, Dina McLeod, Mirella Giudice
(Pharmacists at the Ottawa Valley Regional Drug Information Service, Ottawa General Hospital)

REFERENCES