Proton pump inhibitors in the treatment of acute gastroesophageal reflux disease

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LJ WOROBETZ. Proton pump inhibitors in the treatment of acute gastroesophageal reflux disease. Can J Gastroenterol 1993;7(5):417-421. Although gastroesophageal reflux is perceived as mainly a disorder of motility, the adequate control of gastric acid secretion remains the most effective therapeutic measure for complete healing of esophagitis. The class of drugs termed 'proton pump inhibitors', including omeprazole and lansoprazole, has been shown to resolve symptoms and heal esophagitis to a significantly greater degree than standard \( \text{H}_2 \) antagonist therapy, with absolute healing rates at eight weeks of 90% versus 57%. Omeprazole and lansoprazole are successful in treating esophagitis refractory to conventional \( \text{H}_2 \) antagonist therapy. The use of omeprazole 20 mg/day as first-line therapy in patients where endoscopic esophagitis exists appears cost-effective.

Key Words: 24 h pH, Gastroesophageal reflux disease (GERD), \( \text{H}_2 \) antagonists, Lower esophageal sphincter (LES), Proton pump inhibitor

Inhibiteurs de la pompe à protons dans le traitement du reflux gastro-ösophagien aigu

RÉSUMÉ: Bien que le reflux gastro-ösophagien soit principalement perçu comme un problème de motilité, la maîtrise de la sécrétion d’acide gastrique demeure la mesure thérapeutique la plus efficace pour la cicatrisation complète de l’œsophage. La classe des médicaments appelée « inhibitores de la pompe à protons » comprend l’oméprazole et le lansoprazole. Elle s’est révélée nettement plus efficace à soulager les symptômes et cicatriser l’oesophagite que le traitement classique aux inhibiteurs \( \text{H}_2 \), s’accompagnant de taux de cicatrisation absolue à 8 semaines de 90% versus 57%. L’oméprazole et le lansoprazole réussissent à traiter l’oesophagite réfractaire aux traitements classiques par anti-\( \text{H}_2 \). Le recours à l’oméprazole à raison de 20 mg/jour en traitement de première ligne chez les patients qui présentent une oesophagite à l’endoscopie semble rentable.

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GASTROESOPHAGEAL REFUX DISEASE (GERD) occurs in individuals where there is inappropriately long exposure of the esophagus to acidic gastric contents. The pathophysiology of this condition is complex and still incompletely understood. GERD is perceived to be primarily a motor disorder of the esophagus, with dysfunction of the lower esophageal sphincter (LES) considered to be the most significant underlying abnormality. Despite the spectrum of motor abnormalities that can be seen in GERD, gastric acid is central to the development of mucosal injury and esophagitis. Animal models have shown clearly the direct relationship between the esophageal mucosal injury and the pH of solutions perfused into the esophagus, esophagitis being induced only with solutions of pH less than 1.3 (1). Addition of pepsin will increase the injury but only if the pH is maintained below 2.3 to allow activation of the pepsin. Although the actual pain of esophagitis appears in part related to osmolality, it also appears to be pH dependant. A positive correlation has also been demonstrated between the pH of solutions infused into the esophageal lumen and the time taken
meal, with little reflux occurring nocturnally. Thus, treatment is directed at suppressing the postprandial acid production. H2 antagonists in usual doses have been shown to be relatively ineffective in accomplishing this, whereas the proton pump inhibitors can effectively suppress acid production throughout the day and overcome meal stimulated acid production. With increasingly severe grades of esophagitis, there is an increasing degree of esophageal acid exposure nocturnally. Thus, acid suppression therapy in this group of patients is aimed at suppressing both day and nighttime acid production.

It is clear that individuals who hypersecrete acid, such as patients with Zollinger-Ellison syndrome, are predisposed to the development of esophagitis. However, studies relating the severity of esophagitis to the degree of acid production, as measured by the maximal acid output stimulated by pentagastrin, are conflicting (6,7). It is clear that there exists a subgroup of patients with idiopathic hypersecretion of acid who are more likely to present with esophagitis refractory to standard therapeutic approaches. These individuals are likely to demonstrate incomplete acid suppression on standard antisecretory dosages of H2 antagonists or omeprazole at 20 mg/day and demonstrate continued esophageal reflux on 24 h pH monitoring. They will usually respond to higher than normal doses of antisecretory medication in order to achieve a greater degree of acid suppression. This is most easily accomplished by using a proton pump inhibitor, such as omeprazole 40 to 60 mg/day, that may be divided into a twice a day dosage. This provides an example of tailoring the degree of acid suppression to the severity of the underlying disease.

A meta-analysis of treatment trials of reflux esophagitis by Hunt (8) has demonstrated a positive correlation between the healing rate of esophagitis at eight weeks and the duration in hours that the intragastric pH is maintained above 4.0 (Figure 1). Thus the efficacy of acid suppressive therapy in treating esophagitis can be predicted by its ability to maintain the gastric pH greater than 4.0. The degree of acid suppression induced by various therapies is summarized by Hunt (8) in Figure 2. As observed, the high degree of acid suppression that can be achieved by omeprazole is reflected in its clear therapeutic advantage in healing reflux esophagitis.
PHARMACOLOGY OF PROTON PUMP INHIBITORS

Until recently, acid suppression was directed at blocking the receptors that stimulate acid production, including the acetylcholine and H2-histamine receptors. It became clear, however, that the degree of acid suppression achieved at conventional drug dosages was partial, mainly due to the drugs' inability to block completely postprandial acid production. Thus a new class of therapy, termed the proton pump inhibitors, was developed. The two drugs available in this class include lansoprazole (9) (not yet available in Canada) and omeprazole (10) (Figure 3). These medications control acid secretion by inhibition of the gastric H+,K+ ATPase (the acid pump) which is the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell. As a weak base, omeprazole concentrates in the acid milieu of the secretory canaliculi where it is converted by acid to its active sulphenamide derivative. This subsequently reacts with sulphydryl groups of the acid pump. In this form the drug does not cross cell membranes and is trapped at its site of action. Thus, because of its complete blockage of the final common pathway for acid production, omeprazole provides an effective and specific means of controlling acid secretion regardless of the stimulus, and inhibits both basal and stimulated gastric acid secretion.

EFFICACY IN ACUTE GERD

Because the most important factor in the development of esophagitis is the prolonged and repeated exposure of acid to the esophageal mucosa, it is not surprising that the proton pump inhibitors have had a dramatic impact in the therapy of acute GERD, given the degree of acid suppression that can be achieved. Earlier studies have clearly demonstrated the superiority of omeprazole in doses of 20 to 40 mg/day against that of placebo in patients with esophagitis (11). These have demonstrated a mean four week healing rate of 81% versus 6% on placebo. Heartburn was also improved at four weeks in 75% versus 23%. Comparison has been made of 20 mg and 40 mg omeprazole doses in esophagitis which demonstrated greater healing at four weeks (70% versus 82%), with this therapeutic advantage disappearing by eight weeks (12).

Several comparative studies have been carried out comparing the use of the H2 antagonists cimetidine and ranitidine with omeprazole (13-16) (Figure 4). When comparing ranitidine 300 mg/day and cimetidine 1600 mg/day with a single daily dose of 20 to 40 mg/day of omeprazole, omeprazole was found to have faster and more complete healing of esophagitis and more effective symptomatic control, even at the 20 mg/day dose. A meta-analysis examining a total of 437 patients compared omeprazole 20 mg/day with ranitidine 300 mg/day (17). This showed a four week healing rate of 75% with omeprazole and 45% with ranitidine, with eight week healing rates of 90% and 57%, respectively (P<0.001).

Lansoprazole in doses of 30 or 60 mg/day achieves healing rates of 63% to 84% after four weeks and 85% to 92% after eight weeks in patients with varying degrees of esophagitis, clearly more effective than placebo with eight week healing rates of up to only 53%. Lansoprazole in doses of 30 mg/day demonstrated more prompt symptomatic control and healing of esophagitis at four and eight weeks when compared with ranitidine 300 mg/day. Healing rates for lansoprazole at four weeks was 63% to 84% and at eight weeks was 85% to 92%, in contrast to ranitidine with healing rates of 39% to 52% at four weeks and 53% to 70% at eight weeks (18-20) (Figure 5).

One trial comparing lansoprazole 30 mg/day with omeprazole 20 mg/day revealed no difference in healing rates at four weeks (63% versus 65%, respec-
Figure 6: Effect of a 12 week course of omeprazole 40 mg/day (▲) or ranitidine 30 mg/day (■) on reflux esophagitis resistant to a three month course of H2 antagonist therapy, including cimetidine up to 2400 mg/day and ranitidine up to 900 mg/day.

Short Term Tolerability

The short term tolerability of the proton pump inhibitors has been established in clinical trials, the clinical experience with omeprazole being greater. Solveill (27) reviewed 19,000 patients participating in short term trials of up to 12 weeks and noticed no difference in the incidence and severity of adverse side effects between omeprazole and placebo. No relationship has been established between the omeprazole dose and the incidence of adverse events. Omeprazole interferes with the cytochrome P450 system in the liver, although its effect is less than that seen with cimetidine. It has the potential to inhibit the metabolism of some drugs. This has been shown for agents such as warfarin, diazepam and phenytoin, but does not appear to affect propranolol or theophylline. Omeprazole can be used safely in patients with liver and renal disease without dose adjustment.

Cost Effectiveness of Omeprazole

Because several therapeutic options are now available for the treatment of acute esophagitis, it is important to address the issue of cost effectiveness of various approaches. Clearly the therapeutic goals for acute treatment are to relieve symptoms promptly, heal esophagitis and prevent complications. Although it is clear that proton pump inhibitor therapy is more effective than other medical approaches, regardless of the degree of esophagitis, the question remains as to the appropriateness of the use of proton pump inhibitor therapy as initial treatment. As the proton pump inhibitors have a greater therapeutic advantage in esophagitis of greater severity, it is likely that the initial use of proton pump inhibitor therapy in more severe esophagitis would have a greater cost effectiveness over other medical approaches. Barter (28) has approached the issue of cost effectiveness of omeprazole as initial therapy in a group of patients that includes all degrees of esophagitis as would be seen in a gastroenterologic practice. Using Saskatchewan drug prices as of 1992 and using three therapeutic approaches, the results are summarized for the treatment of 100 patients in regards to cost of therapy (Table 1).

Regimen 1 includes omeprazole (Losec, Astra Pharma) 20 mg/day for four weeks (expected healing rate 60%). Unhealed patients would then receive omeprazole 20 mg for an additional four weeks (expected healing rate 85%). The remaining unhealed patients would receive omeprazole 40 mg/day for an additional eight weeks. The total expected healing rate for these regimens would be 98%.

Regimen 2 includes ranitidine (Zantac, Glaxo) 300 mg/day for four weeks (healing rate 35%). Unhealed patients would receive ranitidine 300 mg/day for a further four weeks (expected healing rate 55%). Unhealed patients

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Estimated cost of treating 100 patients with reflux esophagitis</td>
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<table>
<thead>
<tr>
<th>Regimen</th>
<th>Weeks 1 to 4</th>
<th>Weeks 4 to 8</th>
<th>Weeks 9 to 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Ranitidine</td>
<td>Total cost (for 100 patients)</td>
<td>Total cost (for 100 patients)</td>
</tr>
<tr>
<td>Regimen 1</td>
<td>Omeprazole 40 mg daily</td>
<td>Ranitidine 300 mg bid if not healed</td>
<td>$15,554.88</td>
</tr>
<tr>
<td>Regimen 2</td>
<td>Omeprazole 20 mg daily</td>
<td>Ranitidine 150 mg bid if not healed</td>
<td>$27,169.95</td>
</tr>
<tr>
<td>Regimen 3</td>
<td>Omeprazole 20 mg daily</td>
<td>Ranitidine 150 mg bid if not healed</td>
<td>$18,039.00</td>
</tr>
<tr>
<td>Regimen 2</td>
<td>Omeprazole 40 mg daily</td>
<td>Ranitidine 40 mg daily</td>
<td>$217.33</td>
</tr>
</tbody>
</table>

Cost per healed patient

- Regimen 1: $158.72
- Regimen 2: $377.36
- Regimen 3: $217.33

Cost estimate based on use of generic ranitidine.
would receive ranitidine 600 mg/day for a further eight weeks. The total healing rate with this regimen would be 72%.

Regimen 3 includes generic ranitidine 300 mg/day for four weeks (healing rate 35%). Unhealed patients would receive ranitidine 300 mg/day for a further four weeks (healing rate 55%). Unhealed patients would then receive omeprazole 40 mg/day for another eight weeks. Expected total healing rate would be 83%. It is important to note, however, that efficacy studies using generic ranitidine have not been done.

**REFERENCES**

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