Management of Patients With Nocturnal GERD

This review article contains information not included in the approved US labeling for ZEGERID (omeprazole/sodium bicarbonate), including alternate dosing schedules for treatment of gastroesophageal reflux disease and suggestions of comparative efficacy to other proton pump inhibitors. Please see the full prescribing information for ZEGERID.

Introduction

Gastroesophageal reflux disease (GERD) is defined as symptoms or tissue damage that result from reflux of gastric contents into the esophagus. Although approximately 40% of the US population has intermittent symptoms of heartburn at least once per month the prevalence of GERD is 14%. The 2 patterns of acid reflux are upright (daytime) and supine (nocturnal). Daytime or upright reflux commonly manifests as postprandial heartburn and may be associated with postprandial regurgitation. These symptoms are usually brief as a consequence of the rapid clearance of gastric acid from the esophagus. Daytime reflux has been reviewed elsewhere. This article focuses on nocturnal GERD, specifically addressing its mechanism, complications, diagnosis, and treatment.

Nocturnal GERD occurs when gastric contents reflux into the esophagus while an individual is recumbent. Approximately 80% of patients with GERD have nocturnal symptoms. Nocturnal reflux is often overlooked as a routine, insignificant medical problem that is without consequence. However, because of the increased quantity and decreased clearance of gastric refluxate at night, nocturnal episodes are generally longer and carry an increased risk for complications. McColl et al found that the correlation between the patient’s and the physician’s assessment of symptom control became progressively discordant as the severity of GERD increased. Underestimating the severity of disease can lead to the inadequate treatment of symptoms (especially nocturnal), subsequent complications of GERD, and patient dissatisfaction.

Symptoms

Symptoms of GERD can be classified as esophageal or nonesophageal (Table 1). Nocturnal GERD is particularly important in causing nonesophageal symptoms including asthma, sinusitis, hoarseness, and laryngitis. Although the relationship between asthma and GERD remains poorly defined, Kiljander et al found that treatment with omeprazole reduced nighttime symptoms in patients with asthma. Persistent acid injury to the esophagus as occurs with nocturnal reflux can lead to complications such as erosive esophagitis, peptic strictures, and Barrett’s esophagus (BE). BE is a well-documented risk factor for esophageal adenocarcinoma and has been reviewed elsewhere.

Diagnosis

Nocturnal GERD is usually a clinical diagnosis and directed questioning will identify patients who would otherwise be missed (Table 2). Ambulatory esophageal pH monitoring is considered the gold standard test to confirm a clinical diagnosis of nocturnal GERD. However, the introduction of proton pump inhibitors (PPIs) has caused a paradigm shift favoring an empiric treatment with a high dose of a PPI as both a diagnostic and a therapeutic intervention. Empiric treatment is inappropriate for patients with an extended duration of symptoms or alarm symptoms (eg, dysphagia, unexplained weight loss, signs of bleeding) because this may delay the diagnosis of more significant complications of nocturnal GERD.

Management

The goals of treatment for nocturnal GERD include symptom control as well as...
the prevention and management of complications. First, the clinician should conduct a thorough review of medications that may be contributing to GERD (i.e., calcium channel blockers, nitrates, anticholinergics) and switch the patient to alternative regimens if clinically feasible. Next, the patient’s lifestyle should be addressed and modified (Table 3). Lifestyle modifications are aimed at decreasing the gastric intraluminal pressure, maintaining lower esophageal sphincter tone, and facilitating esophageal clearance of refluxate.

The medical treatment of GERD includes antacids, histamine-2 receptor antagonists (H₂RA), prokinetics, and PPIs. Antacids are over-the-counter medications that act to buffer the gastric pH. However, this effect is short-lived and rapidly reversed by increased production of gastric acid. Given the short duration of effect of these medications, they have a limited significant role in the management of nocturnal GERD.

Acid Suppression

The hallmark of treatment for nocturnal GERD is acid suppression with H₂RAs and PPIs. H₂RAs and PPIs decrease the production of gastric acid, by inhibiting different steps in the acid production pathway. Both H₂RAs and PPIs are effective for initial symptom management in GERD; however, PPI therapy has been shown to be superior to H₂RA therapy in all controlled trials.¹⁵

H₂RAs (e.g., cimetidine, famotidine, nizatidine, and ranitidine) decrease the secretion of gastric acid through competitive inhibition of the histamine-2 receptor of the gastric parietal cells. This effect is short-lived, and tachyphylaxis quickly develops; decreased efficacy with repeated dosing can occur with 3 days.¹²,¹³ H₂RAs induce a modest reduction of gastric acid and may be effective for the treatment of mild symptoms of GERD.¹ Given the concern for tachyphylaxis, H₂RAs may be used on an as-needed basis for breakthrough symptoms.

PPIs have been most effective in managing the symptoms of GERD. All PPIs work by irreversibly inhibiting the H⁺/K⁺-ATPase (proton pump) of the gastric parietal cell. Five PPIs are available: omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. All PPIs have been shown to control symptoms of GERD and heal esophagitis when used in prescription doses.¹ Small variations in the pharmacokinetics or pharmacodynamics of these drugs may explain occasional interpatient variability in their efficacy. Because all PPIs are acid-labile, they are ineffective when given by mouth unless protected from gastric-acid. Thus, all PPIs were originally formulated as enteric-coated (delayed-release) preparations. The enteric coating allows the PPIs to withstand exposure to gastric acid and subsequently be degraded and absorbed in the small intestine. The required degradation of enteric coating prior to absorption causes a significant delay in peak plasma concentrations.

The proper timing of PPI dosing is critical to optimal drug effect. Blockade of the proton pump depends on the presence of adequate concentrations of PPI at the gastric parietal cells at the time of dynamic proton pump activation, as occurs with ingestion of a meal. Studies have shown that delayed-release PPIs are most effective when taken before a meal.¹⁹ All delayed-release PPIs should be taken 15 to 60 minutes before a meal. A survey of patients with poorly controlled GERD who were referred to a gastroenterologist for management of their condition, found that a majority of patients (54%) were taking their PPIs incorrectly.²⁰ A simple, yet very effective strategy in managing “refractory” GERD is to advise patients to take their PPI before a meal.

Further medical management includes the stepwise adjustment of PPI medication including alternate use, increased dosage, and increased dose frequency to achieve symptomatic control. Antacids and H₂RAs should be used only as adjunctive therapy for moderate to severe GERD. An increase in the use of antacids or H₂RAs should alert clinicians to the need to adjust PPI dosing. Symptoms may be relieved if PPI is dosed once daily before the evening rather than the morning meal or if the dosing is increased to twice daily, with the medication taken before both breakfast and dinner. A treatment algorithm for the management of nocturnal GERD appears in the Figure.

Nocturnal acid breakthrough is defined as a nighttime gastric pH of less than 4.0 for longer than 60 minutes despite PPI treatment once or twice daily. This pharmacologic phenomenon has been reported with all delayed-release PPIs. Possible explanations include increased synthesis of H⁺/K⁺-ATPase or the recruitment of presynthesized proton pumps stored in cytoplasmic vesicles that replenish luminal proton pumps. The clinical significance of nocturnal acid breakthrough remains controversial, yet, if reflux occurs in the absence of nocturnal acid breakthrough it would likely be less injurious. Thus, the prevention of nocturnal acid breakthrough may be a goal of adequate acid suppressive therapy in patients with nocturnal GERD. Nocturnal acid breakthrough occurs early after recumbency (10:00 PM-2:00 AM) in patients who take a PPI once daily before breakfast, whereas in patients who take a PPI twice daily, nocturnal acid breakthrough occurs 6 to 7 hours after the evening dose.²³ Hatlebakk and colleagues showed that taking a PPI before the evening meal decreases the incidence of nocturnal acid breakthrough.²⁴

Recently, an immediate-release (IR) formulation of omeprazole has become available that is a combination of non–enteric-coated omeprazole combined with sodium bicarbonate (IR-omeprazole). The bicarbonate buffers the pH of the gastric contents, thus preventing the degradation of omeprazole. The intact omeprazole is absorbed more quickly, so that peak plasma concentrations are reached within approximately 30 minutes rather than the 1 to 2 hours required with delayed-release PPIs.²⁵ The bicarbonate may also stimulate the secretion of gastric acid by activating the proton pump, enhancing the effect of the drug. The new IR-omeprazole may be taken independently of meals, so that bedtime dosing is possible. Castell and colleagues have shown that a single bedtime dose of 40 mg of IR-omeprazole is superior to the once-daily (before dinner) or twice-daily (before breakfast and dinner) dosing of 40 mg pantoprazole in reducing nocturnal acid breakthrough.

---

**Table 3. Lifestyle Modifications for Nocturnal GERD**

<table>
<thead>
<tr>
<th>MECHANICAL APPROACHES</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation of head of bed (6-8 inches)/sleeping on wedge or pillows</td>
<td>Gravity-mediated decreased reflux and improved clearance</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Reduces external compression</td>
</tr>
<tr>
<td>Sleep on the left side</td>
<td>Pools gastric contents on greater curvature of gastric body and antrum</td>
</tr>
<tr>
<td>Avoid tight-fitting clothes</td>
<td>Reduces external compression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DIETARY MODIFICATIONS</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in postprandial recumbency for 2-3 hours</td>
<td>Decreases intraluminal pressure and volume</td>
</tr>
<tr>
<td>Avoid carbonated beverages</td>
<td>Reduces belching</td>
</tr>
<tr>
<td>Avoid alcohol, chocolate, peppermint, raw onions, coffee, fatty foods</td>
<td>Agents that decrease lower esophageal sphincter tone</td>
</tr>
<tr>
<td>Avoid trigger foods: spicy, acidic, etc.</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROMOTION OF SALIVARY PRODUCTION</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>Tobacco use reduces salivary volume and bicarbonate</td>
</tr>
</tbody>
</table>

**Supported and approved by Santarus, Inc.**

---
while maintaining equivalent 24-hour control of the mean gastric pH. Forty milligrams of IR-omeprazole at bedtime is also more effective than 30 mg of Lansoprazole or 40 mg of Esomeprazole taken at bedtime in controlling nocturnal acid breakthrough. Given its rapid onset of action, potency, and ability to control nocturnal acid breakthrough, IR-omeprazole is a very effective new option for the treatment of nocturnal GERD.

**Conclusion**

Nocturnal GERD is an often underappreciated medical condition that is associated with significant adverse effects. Careful patient assessment with special attention to the symptoms of nocturnal GERD is important to both diagnosing and evaluating the significance of patient’s symptoms. The management of nocturnal GERD should be tailored to each patient with careful attention given to esophageal and nonesophageal symptoms in addition to quality of life. Lifestyle modifications, antacids, and H2RAs may be effective for mild cases of nocturnal GERD; however, most patients will require PPI therapy. Particular attention to dosing, specifically of delayed-release PPIs, before meals is important. Alternate dosing patterns, including taking a PPI before the evening meal, may relieve symptoms. IR-omeprazole can be effective in patients whose nocturnal GERD is inadequately controlled with other regimens or who do not adhere to a regimen of delayed-release PPI dosing. When IR-omeprazole is dosed once daily at bedtime, it is also a cost-effective alternative to a delayed-release PPI dosed twice daily for controlling nocturnal acid breakthrough. Early recognition, patient education, and effective medical therapy are the keys to managing nocturnal GERD and preventing associated complications.

**References**


