Immediate-Release Therapy for Control of Nocturnal GERD

An estimated 20% of the US population experiences symptoms of gastroesophageal reflux disease (GERD) at least once a week,[1] with approximately 80% of patients reporting heartburn at night.[2] Conventional delayed-release proton pump inhibitors (DR-PPIs) do not effectively control nocturnal gastric acidity when dosed once daily before breakfast, once daily before the evening meal, or even dosed twice daily (before breakfast and evening meal).[3] The availability of an immediate-release PPI that may be taken at bedtime offers physicians a new option for managing patients who need nighttime acid control.

Key differences between daytime and nighttime reflux include the timing of GERD symptoms, which may impact the condition's severity and potential consequences. Daytime reflux tends to occur in short bursts after meals, whereas nocturnal reflux episodes, although less frequent, result in more prolonged exposure of esophageal mucosa to gastric acid.[4] The body's ability to respond to acidic gastric refluxate also varies between the day and night. During the day, acid reflux stimulates increased secretion of saliva, which contains bicarbonate, and increased esophageal peristalsis to help promote neutralization of acid and clear gastric refluxate. These physiologic responses are blunted during sleep, resulting in more prolonged exposure of the esophageal mucosa to acid.[5]

Abnormal gastric acid reflux occurs more frequently during the first half of the sleeping or recumbent period. A recently published study of 59 patients with nighttime reflux showed that episodes occurred significantly more often during the first half of the recumbent period than during the second half (median, 6.3 % vs 0.3 %, respectively; $P<0.001$).[6]

Data indicate that patients with GERD found nocturnal symptoms more bothersome than daytime symptoms. Farup and colleagues reported that GERD patients with nighttime reflux reported poorer health-related quality of life than the general population. Almost two thirds of people with nighttime reflux symptoms said that sleep was disturbed, and 40% stated GERD-related sleep impairment affected the ability to function the next day.[7]

Additionally, nocturnal GERD increases the risk of more severe clinical consequences, including erosive esophagitis and esophageal adenocarcinoma.[5] The ability of acid-suppressive agents to maintain intragastric pH >4 correlates significantly with healing of erosive esophagitis.[8] Weekly reflux symptoms correlated with a 7.7-fold increased risk of esophageal cancer compared to non-GERD patients. The cancer risk increased 10.8-fold among patients with nocturnal GERD.[9]

Pharmacologic Treatment

Most patients with GERD try nonprescription medications to control reflux symptoms, but few rate them as effective. Shaker and colleagues reported that 71% of respondents with nighttime GERD reported using over-the-counter treatments, but only 29% considered the treatments completely satisfactory.[2] About 40% of the respondents had used prescription medications to treat GERD, and about half considered the agents completely satisfactory.

A substantial proportion of patients with GERD have suboptimal suppression of nocturnal gastric acid secretion when treated with DR-PPIs. Nearly 70% of patients with GERD who are treated with PPIs have nocturnal acid breakthrough (NAB), defined as gastric pH <4 for more than 1 continuous hour during the night while on PPI therapy.[10,11]

Limitations of DR-PPIs

DR-PPIs have enteric coatings that delay their absorption into the systemic circulation and delay reaching peak plasma levels. PPIs only block actively secreting proton pumps. Hatlebakk and colleagues showed that PPIs, taken 30 minutes before breakfast rather than without breakfast, controlled daytime gastric acidity significantly better, since breakfast was a potent stimulus for activation of proton pumps.[12] Despite this finding, Peghini and colleagues showed that administering DR-PPIs twice daily, 30 minutes before breakfast and the evening meal, failed to maintain control of nighttime gastric acidity in both healthy subjects and GERD patients.[10] Thus, dosing PPIs prior to the evening meal may not be an optimal strategy for suppressing nocturnal acid secretion, especially since more than half of patients fail to adhere to prescribed dosing schedules.[13]

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Clinicians have tried to suppress nighttime gastric acidity by administering H_2RAs at bedtime in addition to PPI therapy. However, recent data demonstrated that administering ranitidine at bedtime along with twice-daily DR-PPI therapy was effective only for the first 3 days of therapy, likely due to the development of tolerance or tachyphylaxis to ranitidine.[14]

Immediate-Release PPI

Immediate-release omeprazole (IR-OME) with sodium bicarbonate (Zegerid®, Santarus, Inc.), available as capsules or as powder for oral suspension, is the first immediate-release formulation of a PPI. Unlike conventional DR-PPIs, IR-OME has no enteric coating. PPIs are generally well-tolerated clinically; the most frequently reported adverse events with IR-OME are headache, diarrhea, and abdominal pain. IR-OME capsules contain 300 mg of sodium per dose, while IR-OME powder for oral suspension contains 460 mg of sodium per dose, which should be considered for patients on sodium-restricted diets.[15]

Pharmacokinetic studies have shown that IR-OME dosed before breakfast reached peak plasma levels of omeprazole significantly faster than DR-OME, 30 minutes versus 90 minutes, respectively. The rapid systemic absorption of IR-OME is associated with a more rapid onset of antisecretory effect. At steady state once-daily morning administration of IR-OME suspension 40 mg demonstrated a prolonged antisecretory effect: median time with gastric pH >4 was 18.6 hours over a 24-hour period. This pharmacodynamic study established that the more rapid onset of antisecretory action does not shorten the duration of acid suppression with IR-OME.[15]

Characterization of the mechanism of action of IR-OME remains incomplete. Evidence suggests that uncoated omeprazole and sodium bicarbonate become rapidly available in the stomach following administration. Sodium bicarbonate neutralizes gastric acid and raises gastric pH > 6.0, protecting uncoated omeprazole from degradation by gastric acid. It has been theorized that the rapid neutralization of gastric acid by sodium bicarbonate may also temporarily stimulate the release of gastrin, thereby activating proton pumps. This allows for proton pumps to be actively secreting when plasma levels of omeprazole are peaking, leading to proportionately greater uptake of omeprazole by parietal cells and greater pharmacodynamic effect because of binding to a greater number of activated proton pumps.[16]

Clinical Trials: IR-OME vs DR-PPI

Recently, two head-to-head, randomized, crossover studies have demonstrated the efficacy of IR-OME in controlling nocturnal gastric acidity when compared to several DR-PPIs in patients with nocturnal symptoms of GERD.[16,17] In the first study,[16] IR-OME 40 mg once daily at bedtime resulted in significantly better control of nocturnal gastric acidity than did the DR-PPI pantoprazole 40 mg given once daily before dinner. Significantly fewer patients treated with IR-OME experienced NAB than did those treated with pantoprazole (53% vs 78 %, respectively; $P<0.005$). Median nocturnal gastric pH and median percentage of time with gastric pH >4 were 4.7 and 55%, respectively, in patients treated with IR-OME vs 2.0 and 27%, respectively, in patients treated with pantoprazole ($P<0.001$).

In the second study,[17] 54 patients with nocturnal GERD were randomized to once-daily doses of IR-OME, lansoprazole, or esomeprazole at bedtime for 7 days. Patients treated with IR-OME achieved an intragastric pH >4 within 15 minutes, compared to 3 hours later in patients treated with esomeprazole and 5 hours later in patients treated with lansoprazole. Also, bedtime administration of IR-OME substantially reduced NAB compared to either esomeprazole or lansoprazole. A significantly smaller proportion of patients had NAB after treatment with IR-OME than those treated with either esomeprazole or lansoprazole (61% vs 92% and 92%, respectively; $P<0.001$, both comparisons). Median gastric pH also was significantly higher with IR-OME during the first half of the night than with bedtime administration of either esomeprazole or lansoprazole (4.34 vs 2.37 and 1.51, respectively; $P<0.001$, both comparisons).

Implications for Clinical Practice

IR-OME achieves rapid and sustained control of nocturnal gastric acidity when dosed at bedtime compared to DR-PPIs. IR-OME offers a viable therapeutic option for patients with nighttime GERD.

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