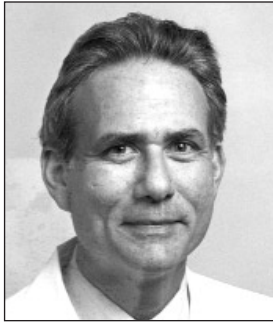


# Nocturnal Reflux: Assessing and Addressing the Problem



Philip O. Katz

Nocturnal gastroesophageal reflux is a common but underappreciated clinical challenge. Although the condition can be asymptomatic, nighttime reflux symptoms can cause sleep disturbances and impact a patient's quality of life; in addition, nocturnal reflux, whether symptomatic or asymptomatic, can lead to complications such as erosive esophagitis and Barrett's esophagus. Proton pump inhibitors are the mainstay of antisecretory therapy for daytime and nighttime gastroesophageal reflux disease, but their effectiveness for achieving nocturnal pH control may be limited by pharmacologic characteristics. Some of these limitations can be overcome by careful attention to the dosing schedule or by adding a histamine H<sub>2</sub>-receptor antagonist at bedtime to proton pump inhibitor therapy. The recent availability of a new, immediate-release formulation of omeprazole—which provides rapid onset of action, fast control of gastric acidity, and sustained control of intragastric pH at steady state—offers intriguing possibilities for the improved management of nighttime heartburn.

## INTRODUCTION

**G**astroesophageal reflux disease (GERD) is defined as the occurrence of chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. The most

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common symptom is heartburn, experienced by 10% of the United States population daily and by 40% at least once monthly (1). In addition, it is estimated that more than 40 million people use over-the-counter antacids and histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>-RAs) at least twice weekly, making GERD a highly prevalent condition. Esophageal reflux usually follows one of two patterns: upright or supine (2). Patients who  
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(continued from page 30)

**Table 1**  
**Nocturnal Heartburn and Reflux**

Nocturnal heartburn

- Important symptom for patients
- Often inadequately treated by physicians
- Negative impact on quality of life

Nocturnal esophageal acid exposure

- Causes nocturnal symptoms and sleep disturbances (e.g., night cough, nocturnal asthma, sleep apnea, recurrent aspiration pneumonia, and pulmonary fibrosis)
- May predispose to long-term complications (Barrett's stricture)

have predominantly postprandial upright, or daytime, reflux usually have symptoms of heartburn or regurgitation, but they are less likely to have tissue damage (erosive esophagitis). Supine reflux usually occurs in the nocturnal or sleeping period, tends towards reflux episodes of longer duration, and is associated with concomitant upright reflux. Complications such as erosive esophagitis, stricture, or Barrett's esophagus appear to occur more frequently in patients with supine or nocturnal reflux.

Nationwide surveys indicate that the prevalence of nocturnal heartburn has been underestimated. It is estimated that more than 27 million Americans have nocturnal GERD symptoms and that 74% of patients with frequent daytime GERD symptoms also experience nocturnal symptoms (2). Two recent surveys encompassing more than 2,200 adults with GERD symptoms at least once a week found that 74% to 79% had some frequency of nighttime heartburn (2,3). Patients who are asleep, usually in a supine position, have diminished protective barriers against GERD. Specifically, the aid of gravity is diminished, esophageal clearance delayed, and salivary flow and swallowing decreased. As a result, nocturnal or overnight reflux may cause multiple sleep-related disorders, as listed in Table 1.

From the patient's perspective, nocturnal acid reflux has a negative impact on quality of life. Recent studies have reported that the majority of patients with nighttime symptoms felt that their ability to get a good night's sleep was affected and that the sleep distur-

bances had a dramatic effect on their daytime activities, including work (2,3). Almost one-third reported that their heartburn-induced sleep disturbances also affected their spouse's sleep. There is clear evidence that nocturnal reflux has a greater impact on quality of life compared with daytime GERD (2). In fact, subjects with GERD reported significantly more pain than those with diabetes and similar pain as those subjects with angina and congestive heart failure (2).

Surveys also indicate that there is poor agreement between clinicians and patients in their assessment of the severity of reflux symptoms, most often reflecting an underestimation of symptom severity by the clinician in relation to the patient's assessment (4). This may be important because it is the physician's assessment of the severity of disease that dictates treatment.

Most patients who experience nocturnal symptoms are not adequately treated (3). A large proportion (71%) of patients with nighttime symptoms report taking over-the-counter medications; however, only 29% felt that these products were completely satisfactory (3). More surprisingly, only about 4 out of 10 persons who have tried prescription medications have found them to be completely satisfactory for relieving nocturnal symptoms (3).

Thus, it is paramount for the clinician addressing a patient with GERD to inquire specifically about the presence of nocturnal symptoms, make an attempt to assess the impact of these symptoms on the patient's quality of life, and tailor a treatment program specifically to address nocturnal reflux. This treatment approach will be discussed below.

## PHARMACOLOGY OF PROTON PUMP INHIBITORS

The backbone of treatment of GERD continues to be antisecretory therapy, principally with proton pump inhibitors (PPIs). In one study of >5000 patients with endoscopically confirmed erosive esophagitis treated with a once-daily, delayed-release PPI, 85% had relief of nighttime heartburn at 4 weeks (5). In contrast, when >3000 patients presenting with frequent heartburn were treated empirically, the percentage of nights when patients reported heartburn was almost 40% after

(continued on page 35)

(continued from page 32)

2 weeks of therapy (6). This ongoing nighttime heartburn despite the daily use of delayed-release PPI therapy may be explained by the pharmacology of delayed-release formulations of these agents.

All PPIs are substituted benzimidazoles, weak bases (pKa approximately 4.5), acid labile, and require protection from gastric acid to prevent degradation before absorption. They are absorbed in the duodenum and converted to the active form, sulfenamide, for transport to the parietal cell, where they block active proton pumps. Enteric-coated formulations of PPIs have a slow onset of action. While some first-day relief is observed, it usually takes 3 to 5 days to achieve a steady-state antisecretory effect. There is individual variability in pH response based on multiple factors such as absorption, cytochrome P450 metabolism, and genetic polymorphism, which may make predicting individual dose response difficult. Because PPIs require pump activation for maximal effect, they are best administered before meals, as maximal activation of the parietal cell occurs in the presence of food (sight, sound, smell, ingestion). For these reasons, delayed-release PPIs achieve the most efficacious control of pH (acid) during the *daytime*, with an almost universal recovery of some acid secretion during the sleep (fasting) period. These pharmacologic characteristics of delayed-release PPIs have important implications for the treatment of nighttime reflux and offer room for improvements in the pharmacology of these agents (Table 2).

### APPROACH TO TREATMENT OF NOCTURNAL REFLUX

The patient with nighttime heartburn represents a clinical challenge to the physician or caregiver in optimizing the use of antisecretory therapy and nonpharmacologic interventions. If nocturnal heartburn is a part of the patient's clinical presentation, I strongly recommend reinforcing one key lifestyle modification: patients should not eat a large evening meal, and specifically should avoid eating dinner within 2 to 3 hours of bedtime. It seems intuitive that a full stomach prior to the hour of sleep will predispose the patient to reflux in the overnight period. A recent study suggests that a 30-minute time window prior to lying down

**Table 2**  
**Criteria for Improving the Current**  
**Delayed-release Proton Pump Inhibitors**

- Reduction in individual variability in pharmacokinetics and pharmacodynamics
- More rapid onset of action
- Sustained control of intragastric acidity
- Improved nocturnal acid control
- Dosing independent of meals

before sleep may be all that is necessary (7); however, until that result is confirmed, patients should be encouraged to maintain the 2- to 3-hour window. Many experts have suggested elevating the head of the bed by 6 inches, as this will facilitate the clearance of nighttime refluxate; however, many patients find this recommendation impractical and difficult to comply with. Alternatively, the patient might attempt to sleep on the left side, as several lines of evidence suggest that reflux frequency in the sleeping period is decreased in this position compared with lying on the right side, prone, or supine (8).

The key to optimal symptom control is effective antisecretory therapy. Maintenance of intragastric pH to  $>4$  is the desired goal, as this will decrease the damaging nature of the gastric refluxate. Delayed-release PPIs are currently the mainstay of antisecretory therapy and can be optimized as follows: If a morning dose of a delayed-release PPI is the first intervention, careful discussion regarding meal timing is crucial to optimize pH control. As mentioned above, the delayed-release PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) require stimulation or activity of the parietal cell for optimal efficacy. The major stimulus for parietal cell activity is food; therefore, I strongly recommend that the PPI dose be given 15 minutes to 1 hour before breakfast. This recommendation is reinforced by a pharmacodynamic study showing a clear improvement in daytime intragastric pH control when a delayed-release PPI is dosed before breakfast compared with a morning dose and no food until noon (9). If the patient does not usually eat breakfast and does not wish to change this lifestyle pattern,

(continued on page 31)

**Table 3**  
**Hierarchy of pH Control**

- PPI once daily
- PPI qam, H<sub>2</sub>-RA at bedtime
- PPI bid
- PPI bid plus H<sub>2</sub>-RA at bedtime

PPI = proton pump inhibitor; H<sub>2</sub>-RA = histamine<sub>2</sub>-receptor antagonist; bid = twice daily before breakfast and dinner.

then administration of the delayed-release PPI should be adjusted to either before lunch or before dinner.

It may be preferable to consider moving the single daily dose of a delayed-release PPI to before the dinner meal, as this has been shown to improve overnight intragastric pH control and decrease nocturnal acid breakthrough compared with the same dose of drug taken in the morning (9). Optimal control of overnight pH with delayed-release PPIs can be assured by splitting the dose and giving the agent twice daily—before breakfast and before dinner (10). This dosing schedule will afford the best overall 24-hour (and nocturnal) pH control.

H<sub>2</sub>-RAs have been used in the laboratory to augment overnight pH control when given at bedtime in conjunction with a delayed-release PPI. Initially evaluated as a “treatment” for nocturnal gastric acid breakthrough, an H<sub>2</sub>-RA (ranitidine 150 or 300 mg) given at bedtime in addition to a delayed-release PPI twice daily has been demonstrated to improve overnight pH control (11). The efficacy of H<sub>2</sub>-RAs is greatest in the first week of therapy, with variability in pH control over time. Studies have shown that tolerance develops after as little as 1 week (12); however, in our observational experience, this regimen will provide long-term efficacy in a substantial number of patients (13). Several pharmacodynamic studies (11–15) have demonstrated a hierarchy of pH control beginning with a PPI before breakfast, adding an H<sub>2</sub>-RA at bedtime, increasing to twice-daily PPI monotherapy, and finally adding an H<sub>2</sub>-RA at bedtime to twice-daily PPI therapy (Table 3). Although nocturnal pH control can be shown to increase incrementally with this approach, there are no published clinical trials showing that symptom improvement is enhanced using any of these regimens

over a PPI alone. Therefore, for optimal efficacy at a reasonable cost, it would be practical to add an H<sub>2</sub>-RA at bedtime to PPI therapy on an as-needed basis.

### IMMEDIATE-RELEASE OMEPRAZOLE

The recent availability of immediate-release omeprazole (IR-OME) powder for oral suspension, a formulation in which non-enterically coated omeprazole is protected from acid degradation by sodium bicarbonate, offers intriguing possibilities for the management of nighttime heartburn. This formulation offers the potential to administer the PPI at bedtime, as opposed to before dinner, and still achieve overnight control of gastric pH. Delayed-release PPIs are generally given before a meal, to take advantage of the activation of proton pumps by food. In the case of IR-OME, it has been postulated that the rapid alkalization of gastric contents by the sodium bicarbonate may activate proton pumps, which, in turn, may be inhibited by the peak plasma concentrations of omeprazole that are reached within 30 minutes of administering IR-OME. Immediate-release omeprazole shows rapid absorption and onset of action, as well as sustained control of intragastric pH at steady state. At steady state (day 7), IR-OME 40 mg maintained intragastric pH >4 for 18.6 hours, and the 20-mg dose did so for 12.2 hours (Table 4) (16). The median intragastric pH was 5.2 and 4.2, respectively (16).

A recently published, randomized, open-label, crossover trial evaluating IR-OME versus delayed-release pantoprazole tablets, both administered to 36 patients with symptomatic nocturnal GERD, reported enhanced control of nocturnal gastric pH with IR-OME at steady state (17). Immediate-release omeprazole 40 mg and pantoprazole 40 mg were administered once daily (at bedtime or predinner, respectively) for 6 days and twice daily (prebreakfast and at bedtime) on day 7. After 6 days, the median percentage of time that gastric pH was >4 for the nighttime interval (10:00 P.M. to 6:00 A.M.) was 55% for IR-OME once daily and 26.5% for pantoprazole once daily ( $P < 0.001$ ; Figure 1) (17). After twice-daily dosing on day 7, the median percentage of time that gastric pH was >4 was 92% and 36.5%, respectively ( $P < 0.001$ ; Figure 1) (17). A

*(continued on page 38)*

(continued from page 36)

**Table 4**  
Effect of Immediate-Release Omeprazole (IR-OME) on 24-Hour Gastric Acidity on Day 7 (Steady State)

Dose	% Time Intra-gastric pH >4	Hours Intra-gastric pH >4	Median pH
IR-OME 20 mg	51	12.2	4.2
IR-OME 40 mg	77	18.6	5.2

Source: Zegerid (omeprazole powder for oral suspension) prescribing information (16).

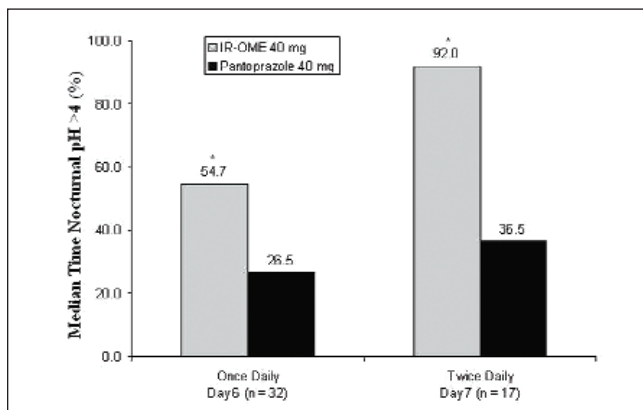
statistically significant difference was also observed when nocturnal pH control rates (i.e., the median percentage of time that gastric pH was >4) for IR-OME 40 mg once daily (day 6) were compared with pantoprazole 40 mg twice daily (day 7) (55% and 34%, respectively;  $P < 0.001$ ). The median nighttime gastric pH values were 4.7 for IR-OME once daily versus 2.0 and 1.7 for pantoprazole once daily and twice daily, respectively ( $P < 0.001$  for each comparison) (17).

The data demonstrated that IR-OME dosed once daily at bedtime reduced nocturnal gastric acidity to an extent not observed with either once- or twice-daily dosing of delayed-release pantoprazole 40 mg. This improved nocturnal pH control suggests that the immediate-release formulation of omeprazole offers a

potential advantage for patients with nighttime heartburn. Our initial experience with IR-OME given at bedtime has been positive; however, more data are needed comparing it with delayed-release PPIs and evaluating its efficacy for nighttime symptom relief.

## SUMMARY

Nocturnal acid reflux is an underappreciated problem. Careful patient assessment is necessary to ascertain its presence and potential impact on a patient's risk for developing complications of GERD and a diminished quality of life. Optimal control of nighttime acid should be sought for patients who have nocturnal symptoms using the principles outlined in this article: careful attention to meal timing, administering a once-daily, delayed-release PPI before dinner rather than before breakfast, giving a delayed-release PPI twice daily, or administering IR-OME once daily at bedtime. As an option, an  $H_2$ -RA may be added at bedtime to delayed-release PPI therapy on an as-needed basis. Compared with delayed-release PPIs, immediate-release omeprazole offers an exciting alternative method of delivering the antisecretory efficacy of a PPI and has been shown to be effective when dosed at bedtime, eliminating the need for a meal to optimize control of nocturnal gastric acidity. ■



**Figure 1.** Effects on nocturnal pH control of repeated dosing of immediate-release omeprazole (IR-OME) 40 mg versus pantoprazole 40 mg. (Left) Both agents given once daily in the evening for 6 days. (Right) Subjects given IR-OME 40 mg or pantoprazole 40 mg once daily for 6 days and twice on day 7, both taken on an empty stomach. \* $P < 0.001$  IR-OME versus pantoprazole. Based on data in Castell DO, et al (17).

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