

Recognition and Management of Nighttime Reflux Symptoms

Background

A majority of patients with gastroesophageal reflux disease (GERD) report nighttime symptoms, including heartburn during sleep. Nighttime reflux is associated with more severe forms of GERD.^{1,2} Multiple studies have demonstrated that nighttime GERD has a substantial adverse impact on sleep and quality of life.^{3,4}

Epidemiology

The vast array of effective therapeutic options for GERD—including antacids, histamine-2 receptor antagonists, and proton pump inhibitors (PPIs)—has until recently obscured the impact of nighttime GERD. A survey of 1,000 GERD patients showed that 79% had nocturnal heartburn, and 75% of those said the symptoms affected their sleep.⁵ In another study, Farup and colleagues⁶ found that 74% of patients with frequent GERD symptoms reported nocturnal symptoms and 54% said heartburn awakened them from sleep. In these studies, most GERD patients had symptoms both during the day and during the night; however, of those, most patients found their nighttime symptoms to be more troublesome. Other studies have documented lower, but still substantial, rates of nighttime GERD symptoms. A community-based study found a 47% prevalence of nocturnal heartburn and a 34% prevalence of nocturnal acid regurgitation.⁷ Data from a large prospective cohort study showed that 25% of participants reported heartburn during sleep.⁸

Characteristics

GERD patients who have symptoms both during the day and at night find nocturnal heartburn more bothersome than daytime symptoms.^{5,6} This might be explained by physiologic differences between the day, when patients are upright, and the night, when patients are generally recumbent. During wakefulness, acid reflux tends to occur more frequently but has a shorter duration compared to reflux during sleep; nocturnal reflux episodes often last substantially longer.⁹ In an animal model of esophagitis, prolongation of acid contact with the mucosa was associated with more severe esophageal lesions.¹⁰

Nocturnal acid breakthrough (NAB) refers to an intragastric pH <4 for at least 1 continuous hour overnight. Initially limited to twice-daily PPI therapy, the definition of NAB has been expanded to include once-daily PPI therapy.¹¹⁻¹³ NAB has been documented in about 70% of healthy volunteers or GERD patients during treatment with a PPI.

Consequences

The presence of nighttime GERD increases the likelihood of various clinical manifestations, such as erosive esophagitis, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma. Additionally, patients with nighttime GERD are more likely to experience extra-esophageal manifestations, such as laryngitis, aspiration, and asthma.^{1,2}

Several studies have documented associations between nighttime GERD and sleep disturbance. A nationwide telephone survey of 1,000 GERD patients,⁵ commissioned by the American Gastroenterological Association, showed that 75% of respondents with nighttime GERD reported altered sleep, and 63% said nighttime heartburn negatively affected their ability to sleep. Additionally, 40% of respondents with nocturnal GERD said the condition adversely affected their ability to function the following day. As the frequency of nighttime GERD increased, so did the likelihood of sleep disturbance.

GERD is a common clinical finding in patients with obstructive sleep apnea (OSA). Moreover, people affected by both conditions have significantly poorer quality of life compared to individuals who have OSA alone.¹⁴



Colin W. Howden, MD
Professor, Division of
Gastroenterology
Northwestern University
Feinberg School of
Medicine, Chicago

patients and a similar degree of pain compared to patients with angina pectoris and congestive heart failure.

Risk Factors

Relatively few studies have examined potential risk factors for nighttime GERD. Nighttime consumption of reflux-provoking meals¹⁵ and body position during sleep have been implicated in some studies.¹⁶

Information gleaned from a US database of 15,700 people showed that greater body mass index (BMI) and younger age were associated with an increased risk of GERD.⁴ Men and college-educated individuals were less likely to report nocturnal GERD, whereas Caucasians and Native Americans were more likely to report this condition. Nighttime heartburn also had positive associations with smoking, hypertension, stroke, asthma, and consumption of carbonated soft drinks. Medications associated with heartburn during sleep included antidepressants, calcium-channel blockers, and benzodiazepines.

In multivariate analyses, the factors that maintained significant associations with nocturnal GERD were college education, higher BMI, carbonated drink consumption, snoring, daytime sleepiness, insomnia, hypertension, asthma, and use of benzodiazepines.⁴

Therapeutic Implications

The development of PPIs has had a dramatic impact on GERD management. Nonetheless, conventional delayed-release PPIs achieve incomplete control of nocturnal gastric acid secretion.¹⁷ Maintenance of intragastric pH >4 throughout the day and night is desirable in order to limit the biological activity of pepsin on the esophageal mucosa; in essence, pepsin is biologically inactive at pH levels >4. As a result, a reflux episode that occurs when gastric contents are at a pH >4 will not have a caustic effect on the esophagus. Furthermore, the ability of acid-suppressing drugs to maintain intragastric pH >4 correlates significantly with their efficacy in healing erosive esophagitis.¹⁸

Delayed-release PPIs have enteric coatings that delay drug absorption into systemic circulation. This results in erratic and unpredictable absorption patterns. Currently, the only PPI without a delayed-release formulation is immediate-release omeprazole (IR-OME) with sodium bicarbonate. When administered as a non-enteric coated capsule or a powder, IR-OME has demonstrated more rapid systemic absorption and a higher mean peak plasma concentration of omeprazole than the conventional enteric-coated/delayed-release formulation of omeprazole.¹⁸

Recently, IR-OME was compared with delayed-release PPIs in two separate studies involving GERD patients with nighttime symptoms.^{12,13} The first study showed

Not surprisingly, given the multitude of potential clinical manifestations, nighttime GERD has a negative impact on quality of life. Farup and colleagues⁶ found that GERD patients with nocturnal symptoms had significantly greater impairment in quality of life than GERD patients who had only daytime symptoms and compared to healthy controls without GERD. Patients with nocturnal heartburn reported significantly more pain compared to diabetic

that IR-OME administered at bedtime produced significantly better control of nocturnal gastric acidity than pantoprazole administered prior to the evening meal. The second study showed that IR-OME dosed at bedtime provided more rapid control of nighttime gastric pH and better control of NAB compared to delayed-release esomeprazole and lansoprazole, also administered at bedtime.

Nonpharmacologic interventions also can aid in the control of nocturnal gastric acidity. Avoidance of carbonated drinks, alcohol, and food for 2 to 3 hours before bedtime can help minimize the chances of nocturnal reflux. Smoking cessation is important for all GERD patients. When indicated, weight loss may also have a beneficial effect on nocturnal GERD symptoms.

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