Nocturnal Acid Breakthrough: Its Physiological Significance and Clinical Relevance

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Nocturnal acid breakthrough (NAB), defined as a drop in intragastric pH to less than 4 for longer than 1 hour during sleep while taking acid-suppressive therapy, is a common occurrence in patients with gastroesophageal reflux disease. During sleep, esophageal acid clearance is diminished, contributing to prolonged acid–mucosal contact during reflux episodes. Although the clinical significance of NAB is a subject of debate, continued gastric acidity presents a risk of esophageal acid mucosal contact during sleep. Use of proton pump inhibitor (PPI) therapy is an appropriate option to consider when developing an optimal plan for the management of NAB and nocturnal reflux. These agents may be incorporated into a step-up plan that begins with standard dosing (once daily in the morning) and progresses, as needed, through several stages, including twice-daily dosing, until control is achieved.

INTRODUCTION

It has been estimated that more than 27 million adults in the United States have nocturnal symptoms of gastroesophageal reflux disease (GERD) (1). The acidic environment of the stomach is an important determinant of response to gastroesophageal reflux (GER), since acid–mucosal contact induces symptoms of heartburn and regurgitation and plays an important role in the development of complications, such as erosive esophagitis. Healing of esophagitis has been shown to be related to the percent of time with intragastric pH >4 (2). Numerous investigations conducted over the last two decades have documented that breakthrough of acid secretion occurs particularly during the sleeping interval (3–8). This may increase the risk of acid reflux during sleep. Thus, effective treatment of GERD requires that the intragastric environment remain nonacidic over a full 24-hour period.

A survey conducted by Farup C, et al found that persons with frequent GERD and nocturnal symptoms had diminished quality of life (QOL) compared with
the general US population (p<0.001) (1). Individuals who had nocturnal symptoms scored significantly lower on QOL measures than those with daytime symptoms (p<0.001), as well as significantly lower than controls (p<0.001) (Figure 1). Sleep-disrupting symptoms were common complaints, the most frequent of which were experiencing GERD symptoms when lying down to sleep (69%) and being awakened at night by symptoms (54%).

Nocturnal acid breakthrough (NAB) is not synonymous with nocturnal heartburn; NAB has been defined as a decrease in intragastric pH to less than 4 for more than 1 hour during the sleeping interval in individuals who are receiving acid-suppressive therapy (9). Nocturnal acid breakthrough can be of concern because it may be associated with acidic reflux. In one study, 66% of the patients who had nocturnal esophageal acid reflux experienced nocturnal heartburn (10).

In patients with GERD who take acid-suppressive therapy, NAB is a common occurrence. Additionally, esophageal reflux occurs during episodes of NAB in 30%–50% of patients (11). Peghini PL, et al showed that NAB occurs both in patients with GERD-related symptoms and in healthy volunteers: 73% of all subjects had episodes of NAB while receiving a proton pump inhibitor (PPI) twice daily (12). All patients with GERD receiving omeprazole 20 mg bid and 50% of those receiving lansoprazole 30 mg bid had NAB. Surprisingly, 69% of the healthy volunteers taking omeprazole 20 mg bid also experienced NAB. Katz PO, et al (9) retrospectively reviewed 113 pH records to determine the prevalence of NAB and associated distal esophageal acid reflux in patients and volunteers who were taking PPIs twice daily. The prevalence of NAB in this study was 69% in patients with GERD, 80% in patients with Barrett’s esophagus, and 68% in healthy volunteers. These differences were not statistically significant, and NAB appeared to occur with equal frequency in patients who took omeprazole and those who took lansoprazole. However, the finding that esophageal reflux occurred during NAB in 31% of patients with GERD, 50% of patients with Barrett’s esophagus, and only 9% of healthy subjects was statistically significant (p<0.03), suggesting that frequency of nocturnal esophageal acid exposure may play some role in disease severity.

**Figure 1.** Age-, sex-, and comorbidity-adjusted Short Form (SF-36) Health Related Quality of Life scores for patients with GERD and control subjects (1). *p<0.001 versus nonnocturnal GERD. †p<0.001 versus controls.
PATHOPHYSIOLOGY OF NAB AND NOCTURAL HEARTBURN

The mechanisms that may contribute to the development of GERD include abnormal esophageal motility, increased transient lower esophageal sphincter relaxations (TLESRs), deficient basal lower esophageal sphincter (LES) tone, impaired clearance of esophageal acid, and, in some cases, impaired gastric emptying (13). During sleep, salivation, swallowing, and consequent peristaltic contractions are significantly reduced. As a result, sleep retards the clearance of esophageal acid, leading to prolonged acid-mucosal contact during sleep-related acid reflux (5,14,15). Nocturnal reflux may be important in the pathogenesis of esophageal damage in esophagitis, extraesophageal manifestations of GERD, and Barrett’s esophagus by allowing prolonged contact of gastric contents with the esophageal mucosa and permitting a greater risk of proximal acid migration.

Currently, the mechanisms producing NAB and nocturnal reflux are unclear. Physiological acid secretion follows a circadian pattern, which peaks around midnight, and histamine may have a major role in nocturnal acid secretion (16,17). Thus, there may be some abnormality in acid secretion that leads to NAB. With regard to nocturnal reflux, Freidin N, et al (3) found that, whereas reflux while patients were awake usually followed TLESRs, this mechanism was responsible for relatively few reflux episodes during the sleeping interval. Other mechanisms of reflux, such as stress-induced and free reflux, were involved only in patients with reflux as compared with control subjects. This suggests that an incompetent LES may play a prominent role in the pathogenesis of nocturnal reflux events in patients with GERD. Fouad YM, et al (15) demonstrated that ineffective esophageal motility and decreased LES pressure were much more prevalent in patients with NAB and abnormal acid exposure during breakthrough (refluxers) than among patients with NAB who did not have abnormal acid exposure during breakthrough (nonrefluxers) (Figure 2). Findings from these two studies suggest that ineffective esophageal motility and decreased LES may increase the risk of nocturnal acid exposure. Even though NAB was common to all patients in this study, NAB itself does not appear to be a factor in potentiating reflux events. Preliminary results from our laboratory have shown that reflux events are no more likely to occur during periods of NAB than during equivalent times without NAB (18).

CLINICAL SIGNIFICANCE OF NAB

The clinical significance of NAB is not clear. However, NAB may increase the likelihood of mucosal injury secondary to reflux events that may occur during NAB (14). Therefore, this could be an important factor in the pathogenesis of erosive esophagitis, peptic strictures, or Barrett’s esophagus—conditions often accompanied by excessive nocturnal esophageal acid exposure during recumbency (9). Fitzgerald RC, et al (19) found that even brief acid exposure might increase proliferation of Barrett’s epithelial cells. Thus, continuous acid inhibition may be helpful in treating Barrett’s esophagus. Recent research also suggests that nocturnal GERD symptoms are an important risk factor for esophageal adenocarcinoma. The risk of

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esophageal adenocarcinoma was 11 times higher among persons in whom heartburn, regurgitation, or both occurred at night at least once a week (20). In addition, nocturnal reflux may play a role in nocturnal asthma and other respiratory complications of sleep-related GER (21-23).

MANAGEMENT OF NOCTURNAL GERD SYMPTOMS

Lifestyle Modification
Management guidelines for GERD frequently advocate lifestyle modifications (24). Modifications include weight loss, elevation of the head of the bed, and eating smaller, more frequent meals. Patients are advised to avoid nighttime meals, caffeine, chocolate, and acidic foods, as well as smoking, lying down after meals, or activities that increase intra-abdominal pressure (e.g., lifting, bending) (24).

However, lifestyle modifications, such as avoiding nighttime meals or raising the head of the bed, may be ineffective for many patients with nocturnal symptoms. In a study of nocturnal reflux in patients with mild-to-moderate nocturnal heartburn, reflux events and sleep-related acid exposure were not significantly different when the patients ate dinner before 7 pm or after 9 pm (25). Only one study has suggested that elevation of the head of the bed can result in improvement in acid exposure, but this was via the mechanism of facilitating acid clearance, not reducing the number of reflux events (26).

PPIs: Agents of Choice for GERD
When choosing among acid-suppressive therapies, symptom control, esophageal healing, and prevention of complications are important goals. Nocturnal reflux is widely considered an important factor in the pathogenesis of reflux disease, particularly in severe esophagitis, in which nocturnal esophageal acid exposure time can last 7 times longer than in mild esophagitis (2). Prolonged reflux events in the supine position (during the sleeping interval) have been shown to distinguish patients with erosive esophageal erosions from those with normal or only an erythematous mucosa (7). Histamine\textsubscript{2}-receptor antagonists (H\textsubscript{2}RAs) can be effective for esophageal healing. However, they often require frequent dosing throughout the day to attain adequate symptom control and are not as effective as PPIs in either measure of treatment success (27). As the most effective acid-suppressive therapy available, PPIs are clearly the agents of choice for treating GERD.

When PPIs are used for control of difficult nighttime GERD symptoms, evening dosing (before dinner) or twice-daily dosing (before breakfast and before dinner) are more effective than morning dosing alone. In a study of the effects of omeprazole 40 mg per day on NAB and gastric acidity in healthy volunteers, NAB occurred in all subjects at baseline and in 78\% of the subjects with only a 40-mg morning dose; however, only 44\% of the subjects taking either the 40-mg evening or 20-mg twice-daily dosing regimen experienced NAB (p<0.05) (28).

A step-up strategy can be applied to patients in whom control of nocturnal GERD has been difficult to achieve. If a patient’s nighttime symptoms are inadequately controlled with a standard dose of a PPI taken once daily in the morning, the clinician first must ascertain that the patient is taking the drug appropriately. Timing before the meal affects PPI absorption and availability (29). A next step may be to have the patient try PPI dosing before the evening meal. The final step up would be to dose the PPI bid. No studies have yet compared before-bedtime dose with an evening-meal dose.

CONSIDERATIONS IN CHOOSING A PPI
Following initiation of standard-dose PPI therapy (omeprazole 20 mg/day, rabeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day, or esomeprazole 40 mg/day), relief of GERD symptoms is attained within several days and healing of esophagitis within 4 to 8 weeks in most patients (30,31). Horn (32) noted that, although all PPIs are similar in structure and method of action, physicians should consider differences in clinical pharmacology when prescribing them. The extent of control of gastric and esophageal pH are important, because esophageal healing in GERD is cor-
related with the duration of acid suppression within each 24-hour period (2). Williams MP, et al (33) demonstrated greater sustained inhibition of acid secretion by rabeprazole than by omeprazole after the first and eighth daily dose, as evidenced by higher 24-hour intragastric pH and longer periods with pH >3 and >4, as well as significantly greater decreases in nocturnal acidity on days 1 and 8. Another study has shown that the half-life of the inhibitory effect of pantoprazole is significantly longer compared with omeprazole or lansoprazole (34). In a study by Lind T, et al (35) esomeprazole 40 mg was found to maintain intragastric pH >4.0 for 70% of the 24-hour recording interval. This was significantly better than 20-mg doses of either omeprazole or esomeprazole. A comparison of rabeprazole 20 mg with esomeprazole 20 mg showed significantly better 24-hour acid control (percentage of 24-hour period with intragastric pH >4) by rabeprazole on day 1 of dosing 47.8% versus 33.2% (p<0.001) (36). On both days 1 and 5, rabeprazole provided significantly better acid control during the time interval of 14–24 hours after dosing compared with esomeprazole (p<0.007). This may convey some advantage to rabeprazole in the treatment of NAB and/or nocturnal GER. Similarly, the long duration of acid suppression noted with pantoprazole may also convey some advantage in dealing specifically with these nocturnal phenomena. There are no studies available comparing any of the PPIs specifically regarding efficacy in treating nocturnal GER.

Control of nocturnal heartburn is another important consideration in the choice of therapy. In the survey by Farup C, et al (1), 69% of respondents with nocturnal heartburn complained of being awakened at night by their GERD symptoms. Compared with the US general population, these individuals experienced decreased QOL because of nocturnal GERD. Assessing the comparative efficacy of these PPIs in relieving complaints of nocturnal heartburn is difficult since none of these studies uses a similar endpoint. Comparative studies examining nocturnal heartburn relief have not been conducted. Most of the PPIs have data that reveal efficacy on some measure of nocturnal heartburn relief. Rabeprazole 20 mg relieved nocturnal heartburn in the majority of patients with GERD after the first dose (37). The percentage of patients who achieved complete or satisfactory (symptom severity reduced to none or mild) relief of nocturnal heartburn during the first week and at week 4 of this 8-week study is shown in Table 1. The proportion of patients with complete and satisfactory relief continued to increase over the course of the trial. Miner P, et al (38) conducted a 4-week, double-blind, placebo-controlled study comparing the efficacy of rabeprazole 10 mg and 20 mg once daily for patients with moderate-to-severe heartburn and endoscopically confirmed nonerosive GERD. Both doses of rabeprazole produced significant relief of nighttime heartburn (p<0.001 vs. placebo) from the first day of administration. About 35% of patients experienced complete relief of nocturnal heartburn after the first dose of either 10 mg or 20 mg of rabeprazole, versus 19% taking placebo (p=0.04). Pantoprazole has been shown to be significantly better than placebo with regard to the median time to "persistent absence" of nighttime heartburn, whereas a comparative study of esomeprazole and omeprazole conveyed a significant advantage to esomeprazole in terms of the proportion of heartburn-free nights (39, 40). Finally, issues of safety and tolerability should be considered when prescribing appropriate acid-suppressive therapy. Both short-term and long-term trials show that PPIs, as a class, are safe and

Table 1.
Complete and satisfactory* relief of nocturnal heartburn in the first 7 days and at week 4 of treatment with rabeprazole 20 mg per day in patients with GERD. Adapted with permission (36).

<table>
<thead>
<tr>
<th>Parameter (%)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Week 4</th>
</tr>
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<tr>
<td>Nighttime complete relief</td>
<td>69.2</td>
<td>78.1</td>
<td>80.9</td>
<td>82.3</td>
<td>83.8</td>
<td>85.8</td>
<td>85.7</td>
<td>90.7</td>
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<tr>
<td>Nighttime satisfactory relief</td>
<td>77.8</td>
<td>88.2</td>
<td>89.6</td>
<td>91.2</td>
<td>91.2</td>
<td>92.5</td>
<td>91.8</td>
<td>95.1</td>
</tr>
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*Symptom severity reduced to none or mild.
well tolerated. Drug–drug interactions with the PPIs are another consideration in prescribing these agents. Metabolism of a PPI depends to varying degrees on cytochrome P450 (CYP) 2C19. The relative contribution of CYP2C19 is greatest with omeprazole and least with rabeprazole (30). Esomeprazole is metabolized to a lesser degree than omeprazole by the CYP2C19 pathway. This is a stereoselective phenomenon. Esomeprazole is the S-isomer of omeprazole, and the S-form has less affinity for CYP2C19 than the R-isomer. Omeprazole, as a racemic mixture of S- and R-isomers, is metabolized by CYP2C19 to a greater extent than esomeprazole due to the stereochemical contribution of the R-isomer (41).

Proton pump inhibitor metabolism can alter metabolism of other drugs, producing interactions. Omeprazole inhibits the metabolism of diazepam, phenytoin, and warfarin. Lansoprazole decreases the concentration of theophylline slightly and may decrease the efficacy of oral contraceptives (32). Rabeprazole has no significant effects on CYP450 isoenzyme systems; it is free of interactions mediated by CYP450 induction or inhibition (42,43). It has been reported that pantoprazole lacks CYP-mediated as well as other types of interactions (43,44). Nevertheless, it is thought that all PPIs reduce blood levels of ketoconazole and raise that of digoxin by altering pH-dependent absorption from the gut (43).

CONCLUSIONS
Nocturnal heartburn is a very common disorder that, according to one estimate, affects about 27 million adults in the United States. Proton pump inhibitors are the preferred agents for treating both daytime and nighttime GERD symptoms. The selection of a PPI regimen is an important therapeutic consideration; this decision involves such factors as the pharmacodynamics and tolerability of different PPIs and the choice of dosing frequency and time of administration.

References


