Nocturnal Acid Breakthrough: A Critical Assessment

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Proton pump inhibitors (PPIs) produce potent gastric acid suppression and are the mainstay of acute and maintenance therapy for erosive and nonerosive gastroesophageal reflux disease (GERD). As a class, these agents generally produce endoscopic healing in more than 90% of patients with erosive GERD (by 8 weeks of treatment).[1,2] Because esophageal exposure to acidic gastric content constitutes a critical element in the pathophysiology of GERD, PPI therapy is given to provide consistent gastric acid suppression to prevent such an event.

Thus far, researchers have reported the occurrence of nocturnal acid breakthrough (NAB)—the presence of gastric pH level below 4 for at least 1 hour during the night—in the setting of high-dose PPI therapy.[3–5] Despite the literature promoting the use of various pharmacologic strategies to prevent NAB, a mounting body of evidence suggests that NAB may not be a useful target for acid suppression in GERD patients with nighttime sequelae because it does not correlate well with gastroesophageal reflux events or nighttime symptoms. These data highlight the need for a more clinically relevant GERD endpoint. The purpose of this paper is to review the current understanding of NAB, to assess the association between NAB and GERD symptoms as well as gastroesophageal reflux events, and to provide suggestions for more reliable clinical and physiologic endpoints to assess GERD management.

NAB AND NIGHTTIME GASTROESOPHAGEAL PHYSIOLOGY

NAB is not synonymous with nighttime heartburn. Heartburn is a symptom, most frequently described as a burning sensation behind the sternum that radiates up toward the throat.[6] In contrast, NAB is exclusively a gastric pH phenomenon (**Figure 1**).[7] Originally, the rationale behind measuring NAB was that the stomach is the source of acid in the refluxate; diminishing or ceasing acid production in the stomach may thus reduce the injurious effect of the refluxate in GERD.

Normal Patterns of Acid Secretion

Perhaps the focus on NAB is driven by an interpretation of the physiology of acid secretion. Normal gastric acid secretion follows a circadian rhythm. Immediately after meals, intragastric pH is elevated by the buffering effect of the food, but the meals also stimulate acid secretion, causing the intragastric pH to drop later. For much of the 24-hour period, the intragastric pH level is below 2.[8] Gastric acid secretion is most pronounced in the evening and early night, resulting in a surge of gastric acidity around 2 AM, with acid secretion decreasing toward the morning.[9,10] Some investigators have proposed that this surge in gastric acidity in patients taking PPI therapy is related to high nocturnal histamine concentration.[4] Thus, GERD patients are naturally predisposed to NAB during the nighttime interval.

Why Night Poses a Special Problem

In patients with GERD, reflux into the esophagus during episodes of NAB is theoretically a cause for concern. Prolonged nocturnal esophageal acid exposure has been shown to contribute to the development of erosive esophagitis.[4,11,12] During the night, reflux episodes are of longer duration because of the loss of gravity-mediated drainage and a significant decrease in swallows. Thus, primary peristalsis and delivery of saliva to the distal esophagus are significantly reduced during sleep.[4] Consequently, nighttime reflux symptoms reported have included heartburn, a bitter or sour taste in the mouth, a burning sensation in the throat, coughing or choking due to fluid or food in the throat, breathlessness, wheezing, and morning phlegm.[13,14] These nocturnal symptoms not only adversely affect sleep, but also impair functional abilities during the day.[15]

Targeting Therapy to Intragastric pH

Early dosing strategies for the treatment of GERD included the administration of histamine receptor antagonists (H_2RAs) at bedtime to combat low nighttime pH levels and nocturnal symptoms. In later studies,

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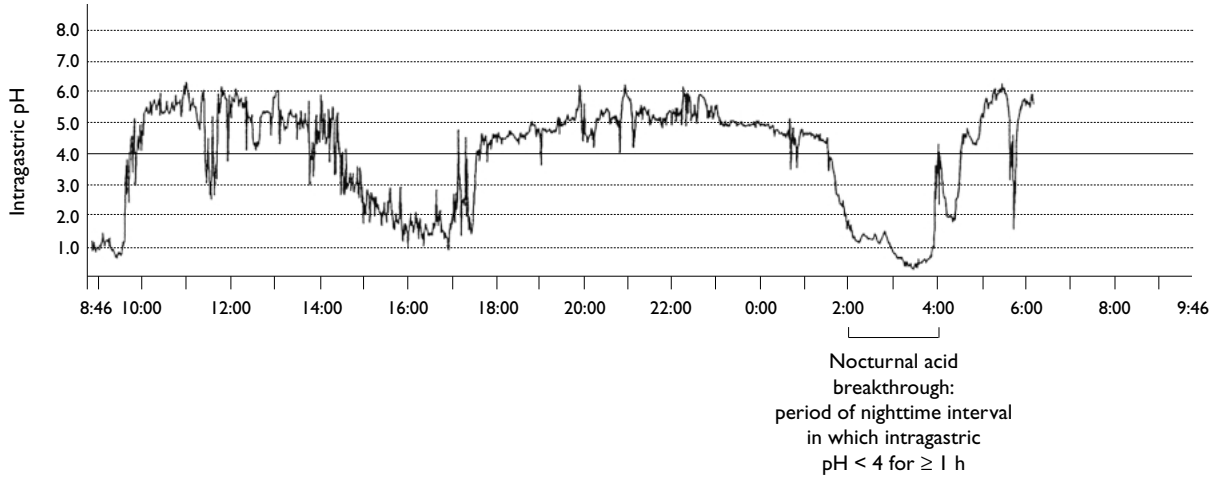

Figure 1. Nocturnal acid breakthrough demonstrated on a 24-hour pH tracing. (Courtesy of Dr. William Orr.)

investigators attempted to use PPIs to improve the control of intragastric pH, demonstrating that although an evening dose of omeprazole substantially increased intragastric pH throughout the day and night, a greater overall effect was achieved with morning dosing.[16] The authors proposed that the benefit observed with an earlier drug administration is likely due to higher intracellular concentrations of the PPI during the daytime period when food intake elicits a greater rate of acid secretion.

Quantification of gastric acidity is a common standard surrogate measure of the efficacy of pharmacologic therapy in GERD.[17] Early studies often relied on median daytime or nighttime pH values in the stomach to measure treatment effect. Decisions based on median pH may be misleading, however, if periods of low pH are counterbalanced by periods of high pH (acid control) to yield a desirable median pH value.[3] Therefore, if periods of increased gastric acidity are of interest, defining a level of acidity over a period of interest (eg, NAB) is a more logical approach to assessing risk for esophageal damage than mean and median pH values.

DEMONSTRATION OF NAB—UNDERSTANDING THE HISTORY

Targeted Therapy

Kuo and colleagues were among the first to show the benefits of dividing the daily omeprazole dose of 40 mg into 20 mg before breakfast and 20 mg before dinner to decrease the amount of time when the gastric pH level was below 4.[18] However, using a twice-daily approach, Peghini and colleagues demonstrated NAB at approximately 7.5 hours following the second daily dose of PPI in patients with GERD who were taking omeprazole 20 mg twice daily, healthy volunteers taking omeprazole 20 mg twice daily, and healthy volunteers taking lansoprazole 30 mg twice daily.[3] In another study involving a group of normal volunteers, omeprazole 40 mg before breakfast, 40 mg before dinner, or 20 mg before breakfast and dinner all reduced the NAB period in the evening, but the twice-daily dosing schedule was significantly superior to the morning or evening dosing schedule ($P < 0.05$). Regardless, in this study, none of the dosing regimens succeeded in eliminating the occurrence of NAB entirely.[4] The authors concluded that omeprazole dosed in the morning does not have sufficient duration of action to provide adequate acid suppression during the nighttime interval.[4]

Investigators also attempted to eliminate NAB by targeting the nighttime histamine surge with H_2RAs. Korn et al[19] added the following medications to a baseline omeprazole regimen (20 mg each morning): a nighttime dose of omeprazole 20 mg; famotidine 10 mg; or famotidine 10 mg plus 21 mEq of antacid, administered 3 hours after the evening meal. More than 50% of the patients still experienced NAB with each of these regimens.[19] In other studies, treatment with varying schedules of a PPI with or without addition of an H_2RA failed to correct gastric pH levels in patients with NAB.[20,21] Furthermore, Ours et al[20] reported that all of their subjects, whether treated with a PPI or a PPI plus H_2RA and regardless of drug schedule, were asymptomatic after treatment despite continuing pH measures indicative of NAB. The authors concluded that NAB is a purely gastric phenomenon with no correlation to esophageal acid levels (also examined in this study) or symptom improvement.

These various studies clearly demonstrate the

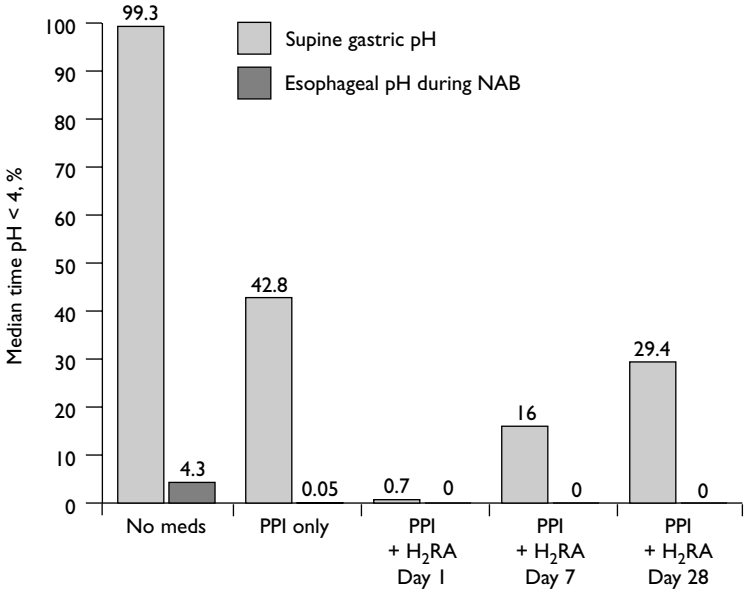

Figure 2. Relationship of supine gastric pH and supine esophageal acid exposure during nocturnal acid breakthrough (NAB) events. Patients (N = 34) were randomized to no medications or proton pump inhibitor (PPI) therapy (omeprazole 20 mg twice daily) with and without a histamine receptor antagonist (H_2RA) (ranitidine 300 mg) for up to 1 month. In this study, all treatment regimens significantly decreased esophageal acid exposure ($P < 0.001$) versus no treatment. After 1 week, NAB increased in patients treated with PPI twice daily and ranitidine therapy, with a further increase seen after 1 month, which is indicative of tolerance to H_2RA. (Data from Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H_2RA therapy on nocturnal gastric acid breakthrough. Gastroenterology 2002;122: 625–32.)

persistence of NAB in both GERD and normal populations despite a range of successful GERD therapies involving PPIs, H_2RAs, and other agents.

NAB and Esophageal Acid Exposure and Subsequent Damage

A study investigating the prevalence of NAB and associated distal esophageal acid exposure in patients receiving twice-daily PPI dosing found that NAB occurred at equal rates among all subjects, including those with GERD, Barrett's esophagus, and normal (untreated) individuals (70%, 80%, and 67%, respectively).[5] In this study, the number of acid reflux events (pH < 4) during episodes of NAB was significantly greater among patients with GERD and Barrett's esophagus than in normal controls ($P < 0.03$). NAB was accompanied by esophageal acid reflux events in 14 of 45 pH assessments (31%) among uncomplicated GERD patients and in 9 of 18 (50%) studies in patients with Barrett's esophagus, but only 2 of 21 (10%) pH studies in normal subjects. Although these data appear to demonstrate a correlation between disease severity and esophageal acid exposure during NAB, the latter occurred with equivalent frequency across all populations studied, and esophageal acid reflux events correlated with NAB in only 31% of GERD patients. Furthermore, the association between NAB, acid reflux, and GERD symptoms was not evaluated in this study. These data suggest that NAB assessment alone would not be a useful predictor of disease severity and, potentially, drug response.[5]

Gastric pH Does Not Predict Esophageal pH

Investigators have studied the relationship between gastric pH and esophageal pH measurements. In a study assessing both intragastric and intraesophageal pH values of patients classified as having either mild-to-moderate esophagitis or severe esophagitis, according to Savary-Miller criteria,[22] subjects with severe reflux esophagitis had a significantly lower gastric acidity level than did healthy controls or subjects with moderate reflux esophagitis.[23] Furthermore, the amount of time that the esophageal pH level was below 4 was significantly longer in subjects with severe esophagitis than in subjects with moderate esophagitis or healthy controls. This study confirms the weak relationship between measures of intragastric acidity and esophageal acid exposure. Similarly, Fackler and colleagues found that the amount of time when the esophageal pH level was below 4 was not prolonged during periods of NAB in patients treated with a PPI twice daily as compared with those treated with a PPI plus H_2RA (**Figure 2**).[7]

In another study, ambulatory 24-hour intragastric and esophageal pH values were compared among healthy patients and erosive esophagitis patients with Los Angeles classification for esophagitis grades A, B, C, and D.[24] As expected, the overall 24-hour esophageal pH, including nocturnal esophageal pH, was higher in patients with greater disease severity. However, intragastric acidity was equivalent across all groups. Although the frequency of reflux episodes across a 24-hour period was the same regardless of disease severity, the number

of reflux episodes lasting longer than 5 minutes was greatly increased in groups presenting with more severe disease.[24] These data reinforce the value of esophageal measurements over intragastric measurements for determining esophageal acid exposure and subsequent mucosal damage. Therefore, decisions on erosive GERD therapy should not be based solely on an agent's effect on gastric pH.

NAB Episodes and GERD Symptoms

Recent studies have shown that NAB events do not demonstrate a temporal relationship with reflux-related symptoms. In 100 consecutive GERD patients who were taking PPIs twice daily, 74% had NAB; only 42% of these patients had reflux nocturnally, whereas the rest did not.[25] NAB was also evaluated in patients with persistent symptomatic GERD despite twice-daily PPI therapy. In this population, 71% (37 of 52) of the patients experienced NAB, but only 36% of these patients had symptoms that correlated with reflux episodes. This finding suggests that gastric NAB is unlikely to account for the failed symptomatic response to PPI therapy.[26] Patients with poorly controlled GERD symptoms despite aggressive pharmacologic management likely have non–acid-related mechanisms for these symptoms, which could be due to altered sensory perception or nonacidic reflux.[25,27]

NAB and Gastric Acid Volume

One of the arguments behind the continued assessment of NAB and intragastric pH (despite lack of correlation with esophageal clinical endpoints) is that it measures the ability of acid suppressive agents to "block" acid secretion at the source (the stomach). However, intragastric pH may not be an accurate marker to assess acid secretion. Because pH is the fraction of acid content over volume, volume is an important factor to consider. Pratha and colleagues found that gastric acid output (calculated as the product of hydrogen ion concentration and gastric volume) correlated more closely to the volume of the gastric aspirate than to gastric pH.[17] Also, pH values vary depending on where the probe is placed in the stomach. Thus, the measurement of pH alone does not reflect gastric output and thus may poorly predict potential acid load during reflux episodes. In addition, volume may be an important factor to consider in the migration of acid. Using a 0.1 N-hydrochloric acid perfusion model in healthy adults, Orr and colleagues[28] found that increasing acid volume was associated with enhanced fluid migration to both mid and proximal esophageal regions as well as significantly prolonged clearance time in the waking state. Sleep, on the other hand, was a significant risk factor for acid migration to the proximal esophagus even for very small acid volumes and it markedly prolonged acid clearance.[28]

NIGHTTIME SYMPTOM CONTROL

As indicated, the relationship between NAB and intraesophageal pH and symptom frequency or severity in GERD is relatively poor. Currently, many authorities no longer accept gastric pH as an outcome measure for PPI therapy and disease control. In addition to traditional healing data, investigators of future studies will need to provide measures of esophageal pH and a greater focus on clinical endpoints such as GERD symptomatology. One such clinical endpoint is esophageal acid exposure (acid contact time), which can be measured through ambulatory 24-hour esophageal pH monitoring. In addition, assessments of the number and duration of reflux events while in the supine position are helpful in predicting reflux disease activity.[11]

From a therapeutic standpoint, lifestyle and diet modifications may improve management of GERD, and patients should be counseled on, for example, dietary measures that can reduce nocturnal gastric acid volume and gastroesophageal reflux. Beginning with an appropriate drug regimen is essential, and uncomplicated GERD patients are normally started on a once-daily dose of a PPI, given in the morning to manage daytime meal-induced gastric acid secretion. Those patients requiring more than a single daily dose of PPI may benefit from a twice-daily regimen—with medication taken before breakfast and before dinner—as this results in better 24-hour gastric acid secretion control compared with a double dose of PPI given once daily.[18] The pharmacokinetic features of various PPIs are compared in the **Table**.

In the past, the addition of an H_2RA at bedtime was recommended for nighttime symptom control, but there is no reliable evidence that this approach affords any benefit over the long term, primarily due to the development of tolerance to these agents.[7,29] Although H_2RAs are uniformly effective for at least 1 week after using them as a therapeutic regimen, tachyphylaxis is common, hampering their long-term usage.

Ultimately, patients with nighttime symptomatology should be monitored closely and compliance with lifestyle modifications as well as drug therapy should be established before considering changes in treatment. Patient compliance with medication is often an overlooked parameter that should be assessed before increasing the dose or altering the timing of medication administration. Patient adherence to the recommended

Table. Comparison of Pharmacokinetics of Proton Pump Inhibitors Available in the United States

Pharmacokinetic Parameters	Omeprazole (20 mg)	Pantoprazole (40 mg)	Lansoprazole (30 mg)	Rabeprazole (20 mg)	Esomeprazole (40 mg)
AUC (μg·h/mL)	0.2–1.2	2–5	1.7–5	0.8	4.32–11.2
C_{max} (μg/mL)	0.8–8	1.1–3.3	0.6–1.2	0.41	4.7
T_{max} (h)	1–3	2–4	1.3–2.2*	3.1†	1.6
$t_{1/2}$ (h)	0.6–1	0.9–1.9	0.9–1.6	1	1.5
Cl (L·h/kg)	0.45	0.08–0.13	0.2–0.28	0.50	9‡
Vd (L/kg)	0.31–0.34	0.13–0.17	0.39–0.46	—	16§
Bioavailability (%) (with repeated doses)	Variable 35→65	Constant: 57–100	Constant: 80–91	—	64–90
Protein binding (%)	95	98	97–99	95–98	97
Dose linearity	Nonlinear	Linear	Linear‖	Linear	Linear
Influenced by:					
Antacids	No	No	Conflicting data	—	No
Renal impaired	No	Conflicting data	Conflicting data	—	No
Hepatic impaired	↑AUC+++	↑AUC+++	↑AUC+++	↑AUC+	↑AUC+++
	↑ $t_{1/2}$+++	↑ $t_{1/2}$+++	↑ $t_{1/2}$+++	↑ $t_{1/2}$+	—
Age (elderly)	↓ Cl	↓ Cl	↓ Cl	—	—
	↑AUC, ↑ $t_{1/2}$+++	↑AUC	↑AUC, ↑ $t_{1/2}$+++	—	↑AUC, ↑C_{max}

AUC = area under the concentration-time curve; Cl = drug clearance; C_{max} = maximum serum concentration; $t_{1/2}$ = elimination half-life; T_{max} = time to maximum serum concentration; Vd = apparent volume of distribution.

*Delayed to 3.5–3.7 h with food.

†Delayed by 1.7 h with food.

‡L/h.

§L, in healthy volunteers.

‖Nonlinear in some studies for doses < 20 mg and intravenous administration.

Adapted with permission from Stedman CA, Barclay ML. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. Aliment Pharmacol Ther 2000;14:963–78.

intake of PPIs in relation to meals must also be ensured for optimal therapeutic effect.[30] In addition, clinicians need to keep in mind that other factors, such as visceral hyperalgesia, motor disorders, and nonacidic reflux, may be responsible for PPI-resistant gastroesophageal reflux.[25]

CONCLUSION

The presence of NAB does not correlate with GERD symptoms, esophageal acid exposure, severity of disease, or symptomatic response to PPI treatment. Additionally, NAB is not the result of PPI failure. Rather than using NAB as a marker of control of nocturnal GERD, health care providers should assess patients based on their clinical presentation and symptomatology, using ambulatory 24-hour esophageal pH monitoring only in the rare cases where information about the degree of acid suppression on PPI therapy is needed (PPI failure). Pharmacotherapy should be targeted toward providing adequate acid suppression to prevent prolonged nighttime esophageal acid exposure. **HP**

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