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Current view

Nocturnal acid breakthrough: consequences and confronting

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SUMMARY

Nocturnal Acid Breakthrough is defined as the appearance of gastric acid in the antrum of pH<4 overnight for a period longer than one hour during the administration of proton pump inhibitors. The prevalence of this phenomenon ranges between 69-79% in normal volunteers and patients with gastroesophageal reflux disease respectively. It typically appears in the second 6-hour period after the evening dose of a PPI when patients are sleeping. The significance of nocturnal acid breakthrough is uncertain despite intense clinical and laboratory investigation. The available data do not lead to firm conclusions, so this interesting matter requires more research in different parts of the world. The relationship between Helicobacter pylori infection and nocturnal acid breakthrough both in health and upper GI disorders disease has not been fully investigated. However, it seems that the Helicobacter pylori status must be taken into account when dealing with nocturnal acid breakthrough, both in patients and normal controls. Despite the fact that data concerning the exact significance of nocturnal acid breakthrough are not conclusive it must be stressed that it is a common phenomenon in proton pump inhibitor therapy. Although esophageal reflux in not a frequent event, it is more likely to occur in patients with poor motility, severe gastroesophageal reflux disease, Barrett's esophagus and scleroderma. It seems that in every day clinical practice, the administration of a proton pump inhibitor before meals and ranitidine at bedtime may well be the most cost-effective method available to control gastroesophageal reflux disease.

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1. INTRODUCTION

During recent years, considerable attention has been paid to so-called Nocturnal Acid Breakthrough (NAB). NAB is defined as the appearance of gastric acid in the antrum of pH<4 overnight for a period longer than one hour during the administration of proton pump inhibitors (PPIs). The prevalence of NAB ranges between 69-79% in normal volunteers and patients with gastro-esophageal reflux disease (GERD) respectively. NAB typically appears in the second 6-hour period after the evening dose of a PPI when patients are sleeping.[1]

The significance of this phenomenon is uncertain despite intense clinical and laboratory investigation. The available data do not lead to firm conclusions, so this interesting matter requires more research in different parts of the world.

In this review, the current data concerning this situation are analyzed and some proposals concerning future research are also suggested.

2. NOCTURNAL ACID SECRETION

In 1987 Kruse-Anderson et al[2] used pH monitoring to evaluate acidic gastroesophageal reflux in patients with duodenal ulcer with and without GERD, as well as in asymptomatic volunteers. Although acid reflux was most prominent during the 3 postprandial hours, GERD patients also had substantial reflux during the 6-hour nighttime period. In normal subjects, 5.5% of reflux occurred during the nocturnal period compared with 37.9% in GERD. Esophageal motility was depressed

during the night in all subjects.

Some years later Sozzi et al[3] further studied nocturnal reflux patterns in patients with and without erosive esophagitis and in normal volunteers. Patients with esophagitis had significantly lower nocturnal gastric pH (1.6 vs 2.2 and 2.6 respectively) and greater esophageal acid exposure at pH<2 during the nocturnal period from 11:00 PM to 3:00 AM. Such data clearly demonstrated that the gastric acidity plays a central role of in the pathogenesis of gastroesophageal reflux.

During recent years it has became clear that the spectrum of GERD has expanded; indeed the majority of individuals with symptomatic GERD do not have erosive reflux disease (ERD); this group has been referred to as nonerosive or negative-endoscopy reflux disease (NERD). There may be important differences between NERD and ERD in terms of pathophysiology and management. Thus, NERD patients appear relatively resistant to proton pump inhibitors (PPIs) and may not be good surgical candidates. Recent twin studies have revealed that genetic factors play a role in GERD and form the basis for future studies on the role of inheritance in the various manifestations of GERD.[4]

Several recent investigations have reaffirmed the primacy of acid reflux in the pathogenesis of GERD and have also provided insights into the pathophysiology of postprandial heartburn. Transient lower oesophageal sphincter relaxations and hiatal hernias have emerged as major and interacting factors in the genesis of reflux episodes and in the potentiation of acid exposure. Moreover, several mouth, laryngeal and lung manifestations associated with GERD have also been described,[5] thus making the significance of gastric acid reflux quite important.

3. PROTON PUMP INHIBITORS AND NOCTURNAL ACID SECRETION

PPIs are considered to be the most powerful antisecretory agents available today. However, Hendel et al[6], in 1995, described low nocturnal gastric pH in many patients receiving a single 40 mg dose of omeprazole for GERD. Patients experiencing nocturnal symptoms seemed to prefer evening dosing, and it was thought that evening administration of omeprazole might provide significantly higher mean nighttime gastric pH compared with morning dosing. However, PPIs may not always effectively decrease nocturnal gastric acid secretion whether given in the morning or at nighttime. Soon it became obvious that nocturnal acid secretion may occur with virtually all PPI regimens because these agents can only inhibit active proton pumps as stimulated by meals.[7]

It well known that PPIs have a relatively short half-life (<2 hours) and their long duration of action depends on their total and irreversible inactivation of active proton pumps during the span of their systemic bioavailability. However, during the night, the morning-dosed PPI is no longer available for blockage of acid secretion by any new pumps that might activate later in the daytime hours after disappearance of active drug from the circulation. Evening administration of PPI without food leads to exposure of the drug to resting proton pumps, and this may result in submaximal efficacy. It is well accepted that predinner PPI dosing is superior to use of PPIs at bedtime; but even the most optimal timing of omeprazole does not fully eliminate nocturnal acid production. This has proven true even with omeprazole twice daily. Some pumps invariably activate during the night after metabolic elimination of the PPI. Such pumps are then available to be stimulated by histamine and/or acetylcholine.

4. NOCTURNAL ACID BREAKTHROUGH (NAB) ON PROTON PUMP INHIBITOR THERAPY

All PPIs available today increase the median 24-hour gastric pH beyond 5.0. However, despite the fact that most patients with GERD respond well to this degree of acid suppression, some require higher or multiple PPI doses. Peghini et al[1] studied twice-daily PPI therapy (omeprazole and lansoprazole) in terms of effect on nocturnal acid breakthrough in 2 groups of subjects: individuals with GERD and normal volunteers. Twenty-four hour pH monitoring identified prominent supine gastric acidity in all subjects. Seventy-three percent of all subjects had NAB within 12 hours (median, 7.5 hours) of the evening dose of PPI. Recovery of nocturnal acid secretion lasting > 1 h, termed acid breakthrough, occurred in three-fourths of all individuals within 12 h from intake of the evening dose of PPI. Median time to acid breakthrough for the whole group was 7.5 h. So, for first time, it became apparent that NAB occurs in the majority of patients and normal volunteers taking PPI b.i.d..

Gastric acid secretion and esophageal reflux are correlated physiologic events. Therefore in order to determine the frequency of NAB and reflux in GERD subjects, Katz et al[8] examined 24-hour pH recordings of 76 patients receiving twice-daily PPIs who had been

referred for pH monitoring. Normal controls, patients with GERD and patients with Barrett's esophagus were included in the analysis. All patients were taking omeprazole 20 mg or lansoprazole twice daily, but continued to manifest GERD symptoms and/or erosive esophagitis. NAB was seen in 70% of 61 patients with gastroesophageal reflux, 80% of 15 patients with Barrett's esophagus and 67% of normal controls (P=N.S.). Oesophageal acid exposure was seen in 33% of GERD patients, 50% of Barrett's oesophagus patients and 8% of normal controls (P < 0.03). So again it was shown that NAB is frequently seen on PPIs twice daily and is sometimes accompanied by oesophageal reflux thus underlying the importance of this phenomenon in symptomatic GERD, erosive esophagitis and Barrett's esophagus having a direct relationship to PPI therapeutic failures. In this setting, NAB of gastric acidity would have no particular importance for patients who do not reflux during intervals of gastric acid production.

Omeprazole has also been evaluated in normal subjects receiving 40 mg before breakfast, 40 mg before dinner, and 20 mg twice daily.[9] NAB occurred in all study subjects being more common on omeprazole 40 mg before breakfast compared with the other dosing regimens. All treatment decreased NAB compared with baseline. The predinner and twice-daily dosing regimens were most effective at reducing NAB, however, it still occurred (median percentage of the nighttime period that gastric pH<4, 31.3% and 20.5%, respectively). The authors suggested that other targeted therapy might be required for full nocturnal acid control in some patients with GERD and that in healthy volunteers dinner time or split dosing of omeprazole 40 mg daily is significantly more effective than dosing before breakfast in preventing NAB and controlling gastric acidity.

In a subsequent study of 100 patients with GERD[10] Foud et al, found that 74% had NAB. Consistently with previous reports, 42% of these patients also had abnormal nocturnal reflux (refluxers) and 58% had no reflux (non-refluxers). The prevalence of ineffective esophageal motility, and low LES pressure was significantly higher in refluxers than in non-refluxers (P < 0. 05, P < 0.001, respectively). Ineffective esophageal motility has a high specificity (91%), but low sensitivity (45%) as a diagnostic predictor for patients who are more likely to develop nocturnal GER on proton pump inhibitor b.d.. Ineffective esophageal motility and decreased LES pressure were significantly more prevalent in patients with abnormal nighttime reflux, suggesting that ineffective esophageal peristalsis is a potential risk factor for the development of NAB despite PPI administration.

5. NAB AND HELICOBACTER *PYLORI* (HP) INFECTION

The pathophysiology of Hp infection on NAB in normal people and patients with GERD and peptic ulcer has not been intensively investigated. It is well known that Hp infection increases the acid-inhibiting effect of PPIs. The Hp status must be taken into account when dealing with NAB both in patients and normal controls.

Van Herwaarden[11], in a small study on normal people Hp positive, found that NAB occurred more often after Hp eradication and that the duration of the longest period with intragastric pH<4 increased significantly after Hp eradication. These data support the assumption that differences in the Hp status may contribute to the explanation of the reported differences in the incidence of NAB in different studies.

In a recent study Kim et al[12] compared the effect of lansoprazole 30 mg twice dayly (bid) to lansoprazole 60 mg once a day (qd) on the prevalence of NAB, to determined whether NAB affects the eradication of Hp in peptic ulcer patients. Sixty-seven patients with Hp-positive peptic ulcers were randomized into two groups, one treated with a combination of lansoprazole 60 mg, clarithromycin 1.0 g, and amoxycillin 2.0 g once a day before breakfast (qd group), and the other, to divided doses of the drugs, before breakfast and dinner (bid group), for 2 weeks. NAB occurred in 31 patients, 55.2% in qd group, and 39.5% in bid group (p =.226). Hp eradication was achieved in 61.3% in NAB positive group and 83.3% in NAB negative group. Differences between the two groups were marginally significant (p=0.055). The mean duration of NAB for Hp eradication group was 99.3+/-22.7 min, and 293.2+/-49.8 min for Hp persistence group (p<0.05). The median intragastric pH of the Hp eradication and persistence group was 5.7+/-0.2 and 4.2+/-0.4, respectively (p<0.05). They concluded that neither the morning dose nor the divided dose regimen of lansoprazole affected the intragastric acidity and occurrence of the NAB. NAB did not influence Hp eradication in peptic ulcer patients, but the duration of NAB and total intragastric median pH were found to influence the Hp eradication.

Katsube et al[13] investigated the prevalence of NAB in Japanese subjects during administration of rabeprazole, and clarified the relationship between Hp infection and NAB. Thirty-one normal male volunteers were examined

by ambulatory 24 h gastric pH monitoring four times: without medication, after a morning or an evening dose of 20 mg rabeprazole, and after admi-nistration of an H2-receptor antagonist at bedtime, in addition to the morning dose of rabeprazole. NAB was observed in 12 patients (39%) after the morning dose of 20 mg rabeprazole. In all cases, NAB was inhibited completely by administration of the H2-receptor antagonist at bedtime. Only one patient with NAB had Hp infection. So, the absence of Hp infection appeared to be closely related to the occurrence of NAB during dosing with a PPI.

6. CONTROL OF NAB WITH BEDTIME H2-RECEPTOR ANTAGONIST THERAPY

Peghini et al[14], in 1998 was first to describe an asymptomatic patient with Barrett's esophagus receiving omeprazole twice daily, who had NAB during 48% of the monitoring period, associated with 23.4% esophageal acid exposure. They found that the addition of ranitidine 300 mg HS in addition to twice-daily omeprazole resulted in decrease of NAB to 22.7% and esophageal acid exposure to 0%.

As a follow-up to this study, the same authors studied 12 normal asymptomatic volunteers taking omeprazole 20 mg twice a day supplemented by 20 mg omeprazole, 150 mg ranitidine, or 300 mg ranitidine at bedtime.[15] An additional dose of omeprazole 20 mg at bedtime significantly decreased NAB from 48% to 31% ($p<0.005$). Alternatively, a morning dose of omeprazole 20 mg plus bedtime ranitidine 150 mg or 300 mg further reduced the nighttime breakthrough to 5% and 6% of the monitoring interval ($p<0.01$) respectively. So, bedtime ranitidine appeared to be more effective than bedtime omeprazole on residual nocturnal acid secretion in patients receiving omeprazole twice daily. It seems that the effectiveness of ranitidine in decreasing this breakthrough supports the hypothesized role of histamine in nocturnal acid secretion and confirms the well-known efficacy of H2Ras in controlling nocturnal acidity, as has been demonstrated during the era of duodenal ulcers.

In a similar study in normal controls[16] taking omeprazole 20 mg twice daily (morning and before the evening meal) and placebo at bedtime vs omeprazole 20 mg before breakfast, placebo at dinner, and 150 mg ranitidine at bedtime, twice daily omeprazole, provided superior acid control vs omeprazole taken with breakfast and ranidinine at bedtime. From these findings, it was concluded that ranitidine at bedtime does not eliminate the need for an evening dose of omeprazole to control intragastric pH in patients requiring more than a single daily dose of omeprazole.

It must be stressed however, that there are data supporting the additive effect of ranitidine at bedtime to the antisecretory effects of omeprazole. In such a study, small OTC dose of ranitidine (75mg) proved as effective as a second dose of omeprazole for control of nighttime gastric acidity.[17] Although it is undoubtedly true that the choice of bedtime omeprazole dosing was suboptimal for acid control, many patients do receive a bedtime dose of PPI in clinical practice, either due to physician ignorance or their own choice of dose timing.

7. VALUE OF H2RA THERAPY FOR THE MANAGEMENT OF NAB

It is well known in a proportion of patients erosive esophagitis remains unhealed on single daily doses of PPIs and many nonerosive esophagitis patients require aggressive antisecretory therapy for symptom control.[18] Because esophageal clearance is impaired at night, the acidity present in the stomach will determine the potential for nocturnal reflux. Therefore, at least for some patients who demonstrate poor healing and/or symptom control due to nocturnal reflux, newer and more effective regimens for the control of nocturnal gastric acidity may be required. Such therapies could include the use of adjunctive measures to deal with NAB associated with PPI therapy. Options entail synergistic H2Ras at bedtime. Only rarely will it be necessary to use multiple daily doses of PPI to adequate control nocturnal acidity and avert NAB.

Robinson et al[19] calculated values for integrated and esophageal acidity over - time in subjects with chronic heartburn. They found that the mean gastric acid concentration fluctuated as a result of ingestion of meals. After six days of treatment with 20 mg omeprazole in the morning, a significant decrease in the integrated gastric and esophageal acidity was noticed. However, morning omeprazole did not eliminate the nocturnal increase in mean gastric acid concentration. The addition of a nocturnal dose of 75mg of ranitidine or 20 mg of omeprazole resulted in the almost complete disappearance of the nocturnal increase in mean gastric acid concentration. A small bedtime dose of ranitidine (75mg) may provide a powerful adjunct to the standard 20-mg morning dose of omeprazole and may, therefore, be worth considering in the "step" therapy of patients who fail to respond to a

single morning PPI dose. It seems that there may still be a place for adjunctive H2RA therapy in PPI recipients. After all, 75mg of ranitidine costs less than one tenth of any currently available PPI and is clear this dose amplifies the pharmacologic effect of omeprazole in GERD. Sonnemberg et al[20] have clearly shown that step-wise therapy of GERD is not only medically sound but such an approach can result in substantial economic benefits.

In a recent study, Orr et al[21] attempted to investigate the occurrence of gastroesophageal reflux and acid breakthrough during polygraphically monitored sleep under conditions of powerful acid suppression with omeprazole 20 mg b.d. and an additional dose of ranitidine at bedtime. They studied 19 patients with symptomatic GERD. Each individual was studied on two occasions subsequent to 1 week of 20 mg of omeprazole treatment b.d. Subjects underwent 24-h oesophageal and gastric pH recording, with polysomnographic monitoring. Patients received either 150 mg ranitidine at bedtime or placebo, prior to a provocative meal. They found that ranitidine administration resulted in a significant ($P < 0.01$) reduction in the percentage of time the intragastric $pH < 4.0$. There was no significant difference with regard to measures of gastroesophageal reflux, and reflux events were not noted to occur with a significantly greater frequency during periods of NAB compared with control intervals without acid breakthrough. The administration of 150 mg ranitidine at bedtime did not significantly alter the occurrence of sleep-related gastroesophageal reflux. However, this study confirmed previous reports claiming that ranitidine significantly reduces the incidence of NAB.

Fackler et al[22] found that the addition of an H2RA to twice-daily PPI therapy significantly reduces the appearance of nocturnal gastric acid. They found however, that this phenomenon was temporary for the majority of people. After 1 week of continuous bedtime ranitidine there was a significant reduction in the acid inhibitory effect yielded by ranitidine on day one. After one month of uninterrupted ranitidine treatment, gastric acidity returned to pre-H2RA levels. However, a proportion of patients seem to respond to bedtime H2RA administration. The authors were not able to find any particular variable to distinquish the responders from the nonresponders. As the authors noticed, intermittent use of H2Ras may provide potential benefit for acid control on an as-needed basis e.g. after a large meal which exposes the esophagus to reflux.

Ours et al[23] evaluated the degree of upright and supine esophageal and gastric acid suppression using various PPI regimens in comparison to the addition of an H2RA at bedtime. A total of 22 subjects (13 with gastroesophageal reflux disease and 9 who served as control subjects) were prospectively evaluated by serial combined esophageal and gastric 24-h pH monitoring. Studies were performed at baseline off antireflux medical therapy and subsequent to completion of 1) omeprazole 20 mg b.i.d. for 2 wk; 2) omeprazole 20 mg b.i.d. plus ranitidine 300 mg HS for 4 wk; 3) omeprazole 20 mg QAM and QHS for 2 wk; and 4) omeprazole 20 mg every 8 h for 2 wk. A dual pH probe was placed 5 cm above and 10 cm below the manometrically defined LES for a minimum of 18 h. Median total, upright, and supine pH values were compared among treatment regimens. All subjects underwent Helicobacter pylori serology testing. Total, upright, and supine median percentage of the time that gastric pH was <4 were significantly less than baseline values in all treatment regimens. Although patients treated with Q8 h omeprazole had significantly ($p < 0.01$) more gastric acid suppression, there was a high degree of overlap among regimens. Treatment regimens resulted in NAB elimination of 9-41%. However, no single treatment regimen resulted in more significant NAB suppression than the others. Despite continued NAB with all treatment regimens, esophageal acid reflux (90%) and patient symptoms (100%) were well controlled. In addition, there were no differences in the esophageal median percentage of time that pH was <4 for any treatment regimen. NAB is an isolated gastric phenomenon that is poorly controlled even with most aggressive acid suppressive therapy. Esophageal acid suppression and symptom control are not dependent on the degree of NAB elimination.

However, despite negative results concerning the significance of NAB, Ours et al,[23] confirmed the observation that NAB is a common event on PPI therapy. Their study was limited to 13 patients, thus making the relationship between gastric and esophageal pH suspect. Xue et al[24] on 45 patients with GERD taking PPI b.i.d. found a significant correlation between the duration of intragastric and intraesophageal times with $pH < 4$ overnight. Because the duration of the study was 30 days, this argues against the hypothesis of "tolerance" to H2Ras. Moreover, Ours et al[22] described the highest percentage of patients (41%) in whom NAB was eliminated occurring in the group receiving PPI twice a day plus bedtime H2RA. Only 9% (2 patients) had NAB eliminated when PPI was given in the morning and at bedtime, a frequent approach in clinical practice.

Adachi et al[25] have recently tried to endoscopically

identify the patients with predominant nocturnal gastroesophageal acid reflux. The subjects were 37 patients with erosive reflux esophagitis (LA grade A, 12; B, 10; C, eight; and D, seven cases) and a control group of 20 patients without esophagitis. The results of ambulatory 24 h gastric and esophageal pH monitoring were compared among different grades of esophagitis. Gastroesophageal reflux during 24 h in patients with high-grade esophagitis was more frequent than for patients with low-grade esophagitis or no esophagitis. The length of esophageal acid exposure (percentage time with pH < 4.0) in patients with grade A or without esophagitis was longer in the daytime, that in patients with grades C and D was longer during the night. The reason for the delayed nocturnal acid exposure was the longer nocturnal acid clearance in high-grade reflux esophagitis. They concluded that nocturnal exposure of the esophagus to acid occurs frequently in patients with LA grades C and D esophagitis. Thus, the existence of NAB with resulting nocturnal acid reflux should be considered when the patient with high-grade esophagitis shows resistance to PPI treatment.

Histamine(2)-receptor antagonists suppress intragastric acidity independently of meals and help to control NAB. Because PPIs require an acid intragastric milieu for activation, nocturnal dosing of H(2)RA might decrease the effect of PPIs taken in the morning by decreasing their gastric-acid-driven activation. Tutuian et al[26] assessed the intragastric acid control on omeprazole, 20 mg, taken every morning, after variable dosing on over-the-counter famotidine, 10 mg. Twelve Hp-negative, healthy volunteers received omeprazole, 20 mg, every morning before breakfast for 15 days. Baseline studies on omeprazole, 20 mg, in the morning, were done on day 7. On nights between days 8-9, 11-12 and 14-15, famotidine, 10 mg at bedtime, and 10 mg at bedtime and/or at 05.30 h, was given in a three-way, crossover, double-blind randomized design. Intragastric pH monitoring was performed on days 9, 12 and 15, starting at 08.00 h. Percentage times intragastric pH < 4 on omeprazole, 20 mg, in the morning of the day after receiving famotidine, 10 mg, at bedtime (58.6 +/- 4.8); at 05.30 h (54.1 +/- 5.1); or at bedtime and at 05.30 h (54.3 +/- 5.0) did not differ significantly (P=0.65) from percentage times intragastric pH on day 7 of omeprazole, 20 mg, in the morning (49.5 +/- 5.1). They concluded that concerns over inhibition of next-day daytime proton-pump inhibitor effect should not preclude use of nocturnal H2RAs in patients with GERD.

In conclusion 1) NAB is a common phenomenon on PPI therapy, 2) esophageal reflux in not a frequent event, although it is more likely to occur in patients with poor motility, severe GERD, Barrett's esophagus and scleroderma, and 3) in everyday clinical practice, the administration of a PPI before meals and a H2RA at bedtime may well be the most cost-effective method to control GERD.[27]

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