Medical Management of Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) is common, with estimates of 20% to 44% of Western populations having symptoms of GERD at least once a month and 20% with weekly symptoms.1 With weekly heartburn or acid regurgitation, the prevalence of GERD in Western countries ranges between 10% and 20%, whereas in Asia the prevalence is less than 5%,2 although there is evidence that GERD is increasing in frequency in several Asian countries.3 The recent Montreal consensus defined GERD as a condition which develops when the reflux of stomach contents causes troublesome symptoms or complications.4 In GERD, a spectrum concept is based on the observation that patients present with or without esophageal mucosal injury. In erosive esophagitis (EE) the esophageal mucosal injury is evident, whereas non-erosive reflux disease (NERD) is defined as “the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy.”4 Functional heartburn is not associated with acid reflux and is defined as retrosternal burning in the absence of GERD that meets other essential criteria for functional esophageal disorders,5 with normal 24-hour pH monitoring (normal/physiologic range of acid exposure).6

GERD presents with a broad spectrum of symptoms, including esophageal and extraspophageal syndromes, which may be mild or severe and which adversely affect the quality of life7 despite the absence of mucosal injury at endoscopy in the majority of patients.8

PATHOPHYSIOLOGY OF SYMPTOMS AND MUCOSAL DAMAGE IN GASTROESOPHAGEAL REFLUX DISEASE

The pathophysiology of symptoms and mucosal damage in EE and Barrett’s esophagus (BE) is currently explained by the increased exposure of the distal esophageal...
mucosa to gastric contents (eg, acid, pepsin, bile acids, and pancreatic enzymes). The degree of acid exposure correlates with the severity of esophagitis and the presence of Barrett’s metaplasia. Heartburn is a symptom complex traditionally accepted as acid mediated and a reliable indicator of GERD; however, these concepts have been questioned because patients with endoscopy-negative heartburn have a lower response rate to acid suppression with proton pump inhibitors (PPIs) than do patients with heartburn and endoscopic changes of EE. Three different mechanisms have been proposed to explain the occurrence of heartburn in the endoscopy-negative setting: (1) esophageal visceral hypersensitivity, (2) sustained esophageal contractions, and (3) abnormal tissue resistance. Abnormal tissue resistance results in activation of esophageal nociceptors by diffusion of luminal acid into (and acidification of) the intercellular spaces. Impaired esophageal mucosal resistance, even to small amounts of acid refluxate, has a key role in the pathophysiology of NERD.

Theoretically, acid can reach the sensory nerve endings in the mucosa by way of dilated intercellular spaces and result in symptoms, which is consistent with the finding that 70% of patients with heartburn do not have endoscopic macroscopic damage of the esophageal mucosa. The precise role of acid in NERD needs to be further clarified.

There has been considerable discussion in recent years over “nocturnal acid breakthrough” (NAB). NAB has been defined as an intragastric pH of less than 4 for more than 1 hour during the nighttime period despite taking a PPI once or twice daily. It is our view that this term is a misnomer, because the observation of pronounced nocturnal acidity has been observed by gastric physiologists for more than 50 years. This situation is also seen in patients taking a PPI owing to the fact that all currently used PPIs have a short plasma half-life (1 to 1.5 hours); therefore, a second dose if given before the evening meal has no effect 5 to 7 hours later, and acid secretion after midnight is not controlled. Moreover, not unexpectedly, NAB occurs in approximately 70% of healthy volunteers and GERD patients. NAB is an intragastric phenomenon and is not necessarily associated with nocturnal intraesophageal acid exposure or nocturnal GERD symptoms, although a low intragastric pH is relevant in patients who have the potential to reflux.

### NOCTURNAL SYMPTOMS AND SLEEP DISTURBANCE

Nocturnal symptoms are frequently reported in reflux patients, and nocturnal acid reflux is associated with more severe mucosal injury, including esophagitis and distal esophageal adenocarcinoma. Nocturnal acid exposure is an important determinant of esophageal mucosal injury. The contact time of an acidic gastric refluxate in the esophagus is greater during sleep than during the day. Nocturnal reflux symptoms have also been reported to have a greater impact on quality of life than daytime reflux symptoms due to a more prolonged esophageal acid exposure time per reflux episode. Nocturnal reflux also has a greater adverse impact on sleep and work productivity.

As many as 40% of GERD patients are not fully satisfied with their antireflux therapy, and approximately 20% of patients require a PPI twice daily in an attempt to control acid secretion in the later part of the day or at night to control symptoms or to heal severe esophagitis. Chey and colleagues found that, when compared with patients without nighttime symptoms, a higher proportion of those with nighttime symptoms took prescription PPIs twice daily (24.3% versus 12.7%, \( P = .008 \)) and were more likely to supplement their PPIs with other GERD medications (45.5% versus 27.9%, \( P = .003 \)). The risk of sleep difficulty increased with nighttime symptom severity.
(odds ratio [OR] of 3.88 for moderate severity and 13.95 for severe/very severe when compared with those with slight severity). Most GERD patients receiving PPIs report nighttime symptoms, with approximately one half having sleep impairment. The risk of incurring sleep impairment and work loss increases with GERD nighttime symptom severity.22

A US Gallup survey of 1000 adults experiencing frequent heartburn found that of the 79% of responders who experienced nighttime heartburn, 75% reported disturbed sleep; for those suffering disturbed sleep, over-the-counter (OTC) medications were “largely ineffective.”23 Although the precise role of acid at night is not clear, the relationship emphasizes the importance of nocturnal acid control, and delayed release PPIs do not adequately control acid secretion in the second part of the day and especially after midnight even when given twice daily.24

An open multinational multicenter trial found that the proportion of GERD patients (n = 633) reporting sleep disturbance before PPI therapy was 84.9%. This percentage fell to 69.6% and 56.9% after 14 and 28 days treatment, respectively, as assessed by the ReQuestTM (self-assessment) questionnaire.25,26 Sleep disturbance appeared to be at least in part acid related because there was a response in about 50% of patients in this study; however, a cause and effect relationship has not yet been studied.

Recent attention has also been drawn to the relationship between obstructive sleep apnea syndrome (OSAS) and GERD. Ing and colleagues27 found that patients with OSAS had more frequent nocturnal reflux than patients without OSAS. On average, patients with OSAS experienced more than 100 reflux episodes during the 8-hour sleep period compared with 23 reflux episodes in controls without OSAS. Esophageal acid clearance was prolonged in OSAS, with a significantly greater proportion of time with a pH less than 4.0 than in non-OSAS controls. Moreover, patients may be awakened by symptoms, leading to deterioration in sleep quality and daytime functioning.28 It has been suggested that OSAS may predispose to nocturnal reflux, because apneic episodes are associated with increased arousals, transdiaphragmatic pressure changes, and low intrathoracic pressures.29

SUPRAESOPHAGEAL REFLUX DISEASE

Symptoms such as hoarseness, globus sensation, chronic cough, and noncardiac chest pain are sometimes called supraesophageal reflux syndromes based on the assumption that they are related to acid reflux. The pooled results from eight studies showed that, overall, PPI therapy resulted in a nonsignificant symptom reduction when compared with placebo [relative risk (RR), 1.28; 95% CI, 0.94–1.74], and no clinical predictors of PPI response were identified on a meta-regression analysis.30 Another meta-analysis including five studies with high-dose PPIs found a pooled RR of 1.18 (95% CI, 0.81–1.74) and concluded that high-dose PPIs were no more effective than placebo for symptom improvement or resolution of laryngopharyngeal symptoms.31 There is insufficient evidence to conclude that GERD treatment with PPIs is universally beneficial for the chronic cough associated with GERD in adults.32 Two studies showed a significant PPI effect,33,34 whereas there was no overall PPI effect in Qadeer’s meta-analysis. Fifty percent of patients in the lansoprazole group achieved a complete symptomatic response compared with only 10% in the placebo group.33 Moreover, clinical improvement was observed significantly more in an omeprazole group than in the placebo group (78.6% versus 18.8%).34 Even though PPI treatment failed to demonstrate a significantly greater improvement in reflux symptoms, health status, or laryngeal appearance, PPIs showed significant improvement in total reflux symptoms when compared with baseline.35 Conclusions on the use of
current PPIs in supraesophageal diseases should be drawn with caution because treatment duration and dosing may be critical factors in determining the outcomes, and studies suggest that some patients may benefit. Studies in these indications using the new generation of antisecretory drugs are awaited with interest.

**DIAGNOSIS: ENDOSCOPIC GRADING, HISTOLOGIC CHANGES, AND PH CRITERIA**

Endoscopic grading is used to evaluate the prognosis in GERD patients. According to current definitions there is no mucosal injury or damage on conventional endoscopy in NERD patients; however, how injury is defined and whether or not mucosal injury exists is debatable and deserves clarification.

As early as the 1970s, the term *minimal change lesion* was first proposed by Ismail-Beigi, and the term was recently incorporated into an endoscopic classification of NERD in Japan. Some studies have employed a modified Los Angeles (LA) classification in which two grades, grade M (minimal changes: erythema, whitish turbidity, or invisibility of vessels) and grade N (normal), are added to the LA grades A, B, C, and D; therefore, NERD might not truly fulfill the descriptor of “normal endoscopic manifestations.” By combining magnification endoscopy and histologic markers, NERD can be predicted with a sensitivity of 62% and a specificity of 74%. The absence of macroscopic injury has shifted attention to the ultrastructural changes in the epithelium. In a study by Zentilin and colleagues, histologic changes were found in 100 of 119 GERD patients (84%) and in 3 of 20 controls (15%) controls, changes that were significant (*P* < .00001). Histology was abnormal in 96% of patients with EE and in 76% of patients with NERD, and a significant correlation (r = 0.426, *P* < .001) was found between the percentage of time with a pH less than 4 and the total histologic “reflux score,” indicating that histologic alterations were mainly due to acid reflux. Dilated intercellular spaces are a feature of NERD, irrespective of acid exposure, and can be considered an objective structural marker of GERD that could be responsible for the enhanced perception of proximal acid reflux. This finding appears to be time reproducible and to represent a sensitive histopathologic marker of NERD.

The effects of PPI therapy on the histologic consequences of GERD are poorly documented. Vieth and colleagues found that after PPI treatment the thickness of the basal layer and length of papillae were significantly reduced in NERD and EE patients, especially in those with LA grades C and D esophagitis, suggesting that proliferative changes of the squamous epithelium in GERD can be reversed by acid secretion, even in severe esophagitis. Calabrese and colleagues found that 3 and 6 months of omeprazole therapy led to a complete recovery of dilated intercellular spaces in 92.1% and 97.4% of cases, respectively; and ultrastructural healing of the esophageal mucosa was accompanied by complete resolution of esophageal symptoms in all cases.

The Johnson and DeMeester scoring system has been the standard to measure acid reflux, although it has some methodologic shortcomings. Twenty-four hour pH monitoring of the distal esophagus quantitates gastroesophageal reflux in a near-physiologic setting by measuring the frequency and duration of acid exposure to the esophageal mucosa. Recently, combined multichannel intraluminal impedance/pH monitoring techniques have been developed to improve the evaluation of symptoms suspected to result from GERD in patients refractory to antisecretory therapy. These techniques allow us to divide reflux episodes into acid reflux (pH <4), weakly acidic (pH between 4 and 7), and weakly alkaline reflux episodes (pH >7). “Non-acid reflux” refers to weakly acidic and weakly alkaline reflux, that is, all reflux episodes during which the nadir esophageal pH does not drop below 4.
PRINCIPLES OF TREATMENT

The purposes of medical therapy for GERD are to relieve symptoms, to heal esophageal mucosal damage, and to prevent the development of complications. Maximizing therapy for the patient with symptomatic GERD is based on an understanding of the multiple lifestyle, pharmacologic, endoscopic, and surgical options for treatment. Although the vast majority of patients can be managed with antisecretory therapy, the optimal use of available agents to maximize efficacy in the difficult or refractory patient requires an understanding of antisecretory pharmacology and pharmacodynamics. According to the American College of Gastroenterology (ACG) guidelines, acid suppression is the mainstay of therapy for GERD. PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest proportion of patients; therefore, PPIs are the first choice for patients who have moderate or severe GERD or complications. In patients with mild GERD, histamine H2 receptor antagonists (H2RAs) given in divided doses may be effective although less so than PPIs.

Treatment of GERD is based on the concept that gastric contents, principally acid and pepsin, are responsible for esophageal mucosal injury and symptoms. The basic principle of pharmacologic management of GERD is the control of intragastric pH, which correlates with esophageal healing and subsequently symptom relief. An algorithm for the management of GERD that can be followed by pharmacists (for OTC medications), primary care physicians, or secondary care gastroenterologists has recently been suggested. This algorithm emphasizes the importance of lifestyle changes to help control the triggers for heartburn and adjuvant therapies for rapid and adequate symptom relief.

OVER-THE-COUNTER DRUG USE

OTC antacids and H2RAs are commonly used by patients with occasional or intermittent reflux or as a rescue therapy in patients already taking prescription treatment. The ACG guidelines consider these agents as appropriate options for patient-directed therapy for heartburn and regurgitation. When symptoms persist, continuous therapy is required; once alarm symptoms or signs develop, the patient should be referred to undergo investigation and treatment.

Over-the-Counter Antacid/Alginate

Alginates have good acid-neutralizing capacity and achieve an elevated pH with a long duration of antacid activity in vitro. In vivo, alginate provides rapid, effective, and long-lasting acid neutralization, with an onset of action of less than 5 minutes and duration of action of almost 90 minutes offering effective treatment for mild symptomatic GERD. A pooled result from four trials found alginate/antacid combinations to be superior to placebo for symptomatic improvement. Antacid/alginate therapy is recommended for self-care medication in patients with mild GERD.

Over-the-Counter Histamine H2 Receptor Antagonists

A systematic review including 10 trials showed a higher response with H2RAs in regards to complete relief of heartburn, symptomatic improvement, and episodes requiring rescue antacids. The absolute benefit increase was 10% to 12% and the relative benefit increase 19% to 41%. These results indicate that OTC H2RAs are effective in treating symptomatic GERD patients.
Over-the-Counter Proton Pump Inhibitors

The availability of OTC PPIs provides consumers with options other than antacids and H2RAs for self-medication of heartburn and acid regurgitation. OTC omeprazole is approved for the treatment of frequent (≥2 days/wk) heartburn.60 The drug should be taken once daily for 14 days and then discontinued. A total of three courses of intermittent therapy may be taken in a 12-month period. For symptoms not responding or requiring more than three courses yearly, it is recommended that the consumer seek further medical advice.60

Fendrick and coworkers61 examined OTC PPI use by making the drug available to consumers at shopping malls in several US cities. A total of 866 participants purchased OTC PPIs, of whom 81% met all criteria for appropriate use. Of 649 participants available for follow-up, 43% stated their frequent heartburn had not recurred. Eighty-six percent of patients in whom symptoms required greater than 14 days of PPI therapy consulted their physician.

INITIAL PRESCRIPTION THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE

Acid suppression is the mainstay of treatment for acute and long-term treatment of GERD.

Erosive Esophagitis

Histamine H2 receptor antagonists

According to the 1995 ACG guidelines,62 the esophagitis healing rate is 50% with H2RAs compared with 24% with placebo. Symptomatic relief can be expected in 60% of patients treated with H2RAs compared with 27% on placebo. It is clear that some patients benefit from H2RAs, and that higher doses and more frequent dosing of H2RAs improve clinical outcomes in GERD.53–65 There is a statistically significant benefit of taking H2RAs compared with placebo for healing esophagitis (RR, 0.74; 95% CI, 0.66–0.84).66 With empiric H2RAs for GERD, the RR for heartburn remission in placebo-controlled trials was 0.77 (95% CI, 0.60–0.99).57

Proton pump inhibitors

Many studies have shown that after 8 weeks of therapy PPIs taken once daily heal 83% to 96% of EE patients regardless of the brand of PPI and the underlying severity of EE.58–71 PPIs heal 74.5% to 84.0% of patients with LA grade C-D disease after 8 weeks of treatment.68 A systematic review and meta-analysis66 including five randomized controlled trials evaluated standard dose PPIs versus placebo over 4 to 8 weeks in 965 patients and found that there was a statistically significant benefit of taking standard dose PPIs when compared with placebo for healing esophagitis (RR, 0.22; 95% CI, 0.15–0.31). A meta-analysis of 10 randomized controlled trials comparing esomeprazole 40 mg once daily with other PPIs found that, at 8 weeks, there was a small but significant increase of 5% in the probability of healing esophagitis in favor of esomeprazole. Esomeprazole 40 mg once daily also conferred a significant improvement of 8% for symptom relief at 4 weeks.72 Another meta-analysis found that the PPI pooled symptom response at 4 weeks was 55.5% (95% CI, 51.5–59.5) in EE patients, with the therapeutic gain being 48.9%.73

A pooled analysis of endoscopic healing by PPIs and baseline LA classification of esophagitis found that the higher the grading, the lower the healing rate of esophagitis (from grade A, B, C to D).68,74 The healing rate at standard doses of PPIs was 40% to 60% for LA grade C and D at 4 weeks and 75% to 85% for grade C and D at 8 weeks.75 A prospective study found a correlation of both healing and symptom relief in EE
patients with grade C and D disease with the percent time the intragastric and intra-esophageal pH was greater than 4.0. The mean percent times with an intragastric pH greater than 4.0 on day 5 in patients with healed and unhealed EE were 61% and 42%, respectively ($P = .0002$), indicating that EE healing rates were positively related to the percent time intragastric pH was greater than 4.0. Greater intragastric acid control correlated with lower final daytime and nighttime heartburn and acid regurgitation symptom scores ($r = -0.029, -0.029$, and $-0.021; P = .003, 0.003$, and 0.032, respectively). Endpoints in clinical trials of GERD include endoscopic healing, which is an objective measure, and relief of symptoms such as heartburn, which is a subjective measure influenced by patient and investigator assessment. In a review of randomized placebo-controlled trials of PPI treatment in GERD, the EE healing rate was significantly higher than the rate of symptom relief, emphasizing the persistence of symptoms even in patients in whom the EE has healed. This persistence makes management decisions difficult and questions whether and for how long continuous PPI therapy is needed. More reliable measures are needed to determine therapeutic response based on improved symptom questionnaires.

**Non-Erosive Reflux Disease**

**Histamine H$_2$ receptor antagonists**

A Cochrane systematic review found that the RR for heartburn remission for H$_2$RAs versus placebo was 0.84 (95% CI, 0.74–0.95) in NERD.

**Proton pump inhibitors**

PPI therapy was better than placebo and H$_2$RA therapy in NERD and undiagnosed reflux symptoms in primary care patients, although the effect was not as large as with esophagitis. The PPI symptom response was only 36.7% (95% CI, 34.1–39.3) in NERD patients, with a lower therapeutic gain of 27.5%. Patients with NERD also demonstrate a longer lag time to sustained symptom response than do patients with EE (two to threefold). Furthermore, patients with NERD demonstrate a similar symptomatic response to half and standard doses of PPI, which is different from EE patients who show an incremental increase in healing and symptom resolution with increased dose.

Patients with functional heartburn demonstrate the lowest symptom response to PPIs once daily when compared with NERD patients. Only 45% of functional heartburn patients report sufficient relief of heartburn symptoms when compared with NERD patients; therefore, the functional heartburn group is likely responsible for the low response rate of NERD patients to PPIs once daily when compared with patients with EE. Functional heartburn patients are also responsible for the lack of any difference seen in symptom response rates between NERD patients on a half-standard dose of PPI once daily and those on a full-standard dose of PPI once daily.

**Barrett’s Esophagus**

Esophageal acid exposure leads to extensive mucosal changes consequent to the inflammatory response and may contribute to the development and progression of dysplasia to BE. EE resulting from extensive reflux, especially in genetically predisposed patients, probably leads to metaplasia which may progress to dysplasia and in some to adenocarcinoma. Many studies have demonstrated that patients with BE have severe acid reflux. When compared with patients who have GERD, patients who have BE are more likely to have a higher degree of pathologic acid reflux despite PPI therapy and less intragastric acid suppression, particularly when supine.
Furthermore, intraesophageal and intragastric pH control is significantly more difficult to achieve in patients with BE. Approximately one quarter of BE patients continue to have abnormal intraesophageal pH profiles despite twice daily PPI therapy. Standard PPI therapy is not associated with normalization of the intraluminal pH of the esophagus in many BE patients; therefore, patients with BE need profound acid inhibition with high-dose PPIs to provide better symptom relief.

Hillman and coworkers investigated 350 BE patients undergoing surveillance (median follow-up of 4.7 years) and found that patients who delayed using a PPI for 2 years or more after the diagnosis of BE had a 5.6 times (95% CI, 2.0–15.7) higher risk of developing low-grade dysplasia at any given time when compared with patients who used a PPI from the first year. Similar results were found for the risk of developing high-grade dysplasia or adenocarcinoma (hazard ratio, 20.9; 95% CI, 2.8–158) and for the use of PPI therapy before the diagnosis of BE, which significantly reduced the presence of markers used to stratify patient risk. Similarly, a retrospective study in BE patients in the United States found that the cumulative incidence of dysplasia was significantly lower among patients who received PPIs when compared with those who received no therapy or H2RAs. Furthermore, among those on PPIs, a longer duration of use was associated with less frequent occurrence of dysplasia. In a multivariate analysis, the use of PPIs after BE diagnosis was independently associated with a reduced risk of dysplasia, with a hazard ratio of 0.25 (95% CI, 0.13–0.47); therefore, all patients with BE, even those with no esophagitis or symptoms, should be encouraged to continue long-term PPI therapy.

CONTINUOUS MAINTENANCE THERAPY FOR EROSAIVE ESOPHAGITIS AND NON-EROSIVE REFLUX DISEASE

Continuous therapy to control symptoms and prevent complications is appropriate because GERD is a chronic condition, and most patients relapse once drug therapy is discontinued, with about 80% of patients experiencing relapse of esophagitis after 6 to 12 months. A systematic review compared the efficacy of PPIs with that of H2RAs over 24 to 52 weeks. For a maintenance dose of PPI (half of the standard dose) versus placebo, the RR for esophagitis relapse was 0.46 (95% CI, 0.38 to 0.57) and versus H2RAs the RR was 0.57 (95% CI, 0.47 to 0.69); for a healing dose of PPI versus placebo, the RR for esophagitis relapse was 0.26 (95% CI, 0.19 to 0.36); versus H2RAs the RR was 0.36 (95% CI, 0.28 to 0.46) and versus maintenance PPIs the RR was 0.63 (95% CI, 0.55 to 0.73); limited data with one RCT for NERD patients showed benefit for omeprazole 10 mg once daily over placebo (RR 0.4; 95% CI, 0.29 to 0.53). These findings support long-term treatment to prevent esophagitis, but more randomized controlled trials in NERD patients are needed to confirm the long-term PPI benefit.

Because patients with NERD are just as symptomatic as patients with EE if not more so, and because endoscopic criteria cannot be applied to evaluate the efficacy of therapy in NERD, successful treatment should be judged by the control of symptoms. Improved symptom-based evaluations should help to evaluate reflux symptoms objectively and monitor precisely how patients respond to therapy, leading to improvements in GERD management.

ON-DEMAND THERAPY

PPI therapy “on-demand” is often used by patients as an alternative to continuous maintenance therapy in GERD. A systematic review including 17 studies concluded that on-demand therapy with currently available PPIs appears to be effective in the long-term management of patients with NERD or mild and uninvestigated reflux
symptoms but not in patients with severe EE. In patients with NERD or mild or un-investigated reflux, control of reflux symptoms should be the main goal of therapy. After initial 2- to 4-week continuous PPI therapy, an on-demand empiric trial of acid secretion with PPIs could be attempted, with the possible exclusion of elderly patients and patients with frequent weekly symptom episodes at the first visit. Despite the results of clinical trials, many patients admit to taking their treatment in an on-demand or intermittent basis.

**MANAGEMENT OF GASTROESOPHAGEAL REFLUX DISEASE REFRACTORY TO PROTON PUMP INHIBITORS**

**Compliance and Timing of Drug Intake**

PPI failure in GERD patients has become the main reason for referral to a gastroenterologist. It is estimated that 30% of GERD patients requiring a PPI once daily will experience treatment failure. Although compliance should not be considered as a cause for PPI failure in patients with GERD, all patients suspected of experiencing treatment failure with a PPI should be initially assessed for compliance. Poor compliance is common among patients receiving PPIs. Oral bioavailability may differ significantly from one PPI to another and may be decreased further when the drug is taken with food or antacids. Moreover, bioavailability has been suggested as a contributory mechanism for failure of PPI therapy.

Patients are advised to take PPI medications 30 minutes before a meal (usually at breakfast) because the meal will stimulate the insertion of acid pumps into the secretory canalicular membrane of parietal cells, providing a maximum number of active pumps to be blocked during the short period of drug availability.

**Effect of Food Intake on the Efficacy of Proton Pump Inhibitors**

PPIs inhibit gastric acid secretion by selectively and noncompetitively inactivating the H⁺, K⁺ ATPase of the parietal cell, but only pumps that are actively secreting acid and not those at rest in the cytosol of the parietal cell. This mechanism implies that stimulation of acid secretion by a meal is necessary for maximal inhibition of gastric secretion. In general, actively secreting ATPase is best inhibited when the dose is given 30 to 60 minutes before a meal, usually before breakfast. A cross-over study showed statistical improvement in intragastric pH control when the dose was given before the meal rather than in the morning with no food until noon. Immediate release omeprazole (IR-OME) eliminates the need for such meal timing, but it remains to be seen whether this drug taken before bedtime will result in improved clinical outcomes. There is still a need for an agent with maximal efficacy irrespective of the time of administration or food intake.

**Adding Bedtime Histamine H₂ Receptor Antagonists to Proton Pump Inhibitor Therapy**

Adding an H₂RA at bedtime to PPI therapy to control nighttime symptoms has been popularized since the late 1990s, but considerable controversy exists regarding this approach. Some studies indicate tolerance to H₂RAs, whereas others have suggested long-term acid control can be maintained with nighttime H₂RA use. Because of H₂RA tolerance, there is no difference in acid suppression between PPIs taken twice daily and PPIs taken twice daily plus H₂RAs after 1 week of combination therapy despite an initial response. Moreover, esophageal acid suppression and symptom control are not dependent on the degree of NAB elimination. Although adding an H₂RA at bedtime to PPI therapy may help some individual patients, treatment will most likely be of benefit when used intermittently.
Failure of Proton Pump Inhibitors

Due to the importance of PPI failure as a target for future drug development, it is necessary to further understand the most relevant underlying mechanisms. PPI failure has been defined as the failure to obtain complete esophageal healing or satisfactory symptom response after a full course (4 weeks for NERD and 8 weeks for EE) of standard dose PPIs (once a day).97 This definition allows the inclusion of patients who perceive their remaining symptoms on PPI therapy as bothersome, independent of frequency or severity.

According to recent surveys, only 40% to 58% of GERD patients are fully satisfied with their antireflux medications, although there is no universal definition of PPI failure.97,98 Various mechanisms have been suggested to underlie PPI failure in GERD patients. The most pertinent include uncontrolled acid secretion and reflux, weakly acidic reflux, duodenogastroesophageal reflux, visceral hyperalgesia, delayed gastric emptying, psychologic comorbidity and concomitant functional bowel disorders, as well as others.90 Treatment relies primarily on escalating dosing of PPIs; however, for the reasons outlined previously, this has little effect on nocturnal acidity.

Most patients who have PPI failure are likely to originate from the NERD phenotype. Patients with NERD are the most common GERD-related group in which once daily PPI therapy fails. Furthermore, patients with NERD demonstrate a direct relationship between the response to PPI therapy and the degree of esophageal acid exposure. A greater proportion of NERD patients who report a symptom response correlates with a greater pretreatment distal esophageal acid exposure11 The opposite results are observed in patients with EE, in whom the greater the esophageal inflammation, the lower the response rate to PPIs once daily.

Proton Pump Inhibitor Refractory Gastroesophageal Reflux Disease

PPI refractory GERD refers to reflux symptoms that fail to respond to twice daily PPI treatment for 4 to 8 weeks in approximately 25% of GERD patients.99 In PPI refractory GERD, either the symptoms or the mucosal lesions or both do not disappear on treatment with a PPI. Our recent meta-analysis indicated a rate of unhealed EE (failure rate) with available delayed release PPIs at standard doses of 40% to 60% for LA grade C and D at 4 weeks and 15% to 25% for grade C and D at 8 weeks.75 In cases of PPI refractory GERD, a careful history may reveal information suggesting that the patient’s symptoms are not related to gastroesophageal reflux and that an alternative diagnosis is more likely.

Patients who have refractory GERD should undergo upper gastrointestinal endoscopy to exclude entities such as peptic ulcer disease or cancer and to identify the presence of esophagitis. Refractory reflux in patients who have normal endoscopy findings are more problematic to manage.99 Currently, patients who have GERD symptoms do not undergo initial endoscopy unless they have dysphagia, bleeding, or weight loss. Instead, these patients are given an empiric 4- to 8-week trial of a PPI to be taken in the morning before breakfast. Failure to respond to such a treatment trial occurs in 25% to 40% of patients.98 For these patients, the physician should confirm patient compliance and check whether the patient is taking the PPI correctly. When patient compliance and the correct timing of the PPI dose have been confirmed yet symptoms persist, it is reasonable to switch to a twice daily PPI. If the history confirms that the patient sustains typical reflux symptoms, an upper gastrointestinal endoscopy is often performed. This study can detect mucosal erosions typical of reflux or point toward an alternative diagnosis. If endoscopy shows no abnormalities, NERD or functional heartburn should be considered. Esophageal 24-hour pH-metry
may be considered. An advantage of performing the study off PPIs is the possibility of determining whether a patient truly has reflux disease. The advantage of performing pH-metry on PPI is to determine whether there is adequate acid suppression and whether symptoms are reflux related. Other available technologies, such as esophageal manometry, impedance monitoring, or capsule pH testing, may help to make the diagnosis in patients who have non-reflux disease. An accurate diagnosis should be established before further treatment. Correct dosing with the PPI and consideration of a drug such as baclofen (which is not yet indicated) may offer an alternative approach for refractory patients.

ENDOSCOPIC AND SURGICAL TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

At least 20% to 30% GERD patients are refractory to PPI or other medical therapy. Endoscopic therapy and antireflux surgery are an alternative option for selected patients with well-documented GERD. Although satisfactory outcomes have been achieved from surgical treatment, patients often need long-term acid suppression after antireflux surgery because of persistent pathologic reflux and acid exposure. Neither endoscopic therapies nor surgery should be considered as “routine” for the treatment of GERD without careful assessment and consideration of their respective merits for an individual patient and without prior assessment of the disease burden.

NEW FORMULATIONS OF PROTON PUMP INHIBITORS

The availability of the newest PPI, IR-OME, offers a different PPI option for the management of nighttime heartburn. IR-OME is a new formulation of “naked” omeprazole without an enteric coating and with added sodium bicarbonate, which provides protection against degradation of the drug by gastric acid. A rapid rise in gastric pH within 15 minutes resulting from the sodium bicarbonate may stimulate gastrin release, which would activate and enhance insertion of proton pumps into the secretory canalicular membrane. This effect is independent of food intake and results in rapid control of acid secretion. IR-OME 20 mg given before breakfast for 7 days raised the intragastric pH to greater than 4 for 51% of a 24-hour period and with a dose of 40 mg for 77% of the time. After 6 days of once daily bedtime administration of IR-OME 40 mg in patients with nighttime heartburn, intragastric pH significantly increased when compared with that on day 1; the median pH increased from 1.1 to 4.7; the percentage of time the pH was greater than 4 increased from 18.4% to 54.7%; and the percentage of patients with NAB decreased from 87.5% to 53.1%. In addition, bedtime IR-OME provided more rapid control of nighttime gastric pH and decreased NAB when compared with esomeprazole and lansoprazole. To date, no outcomes studies have been undertaken with this drug, although it might provide a more effective and faster way to relieve heartburn, especially in patients with nocturnal symptoms or those who need on-demand therapy. Adverse effects should be considered before prescription because IR-OME contains 1100 to 1680 mg of sodium bicarbonate per tablet or capsule (20 or 40 mg), which may aggravate hypertension and congestive heart failure.

TAK-390MR is a dual delayed release formulation of an enantiomer of lansoprazole with double plasma peaks which is associated with a longer half-life and subsequently prolonged intragastric pH control. In a cross-over study of 40 healthy subjects, TAK-390MR for 5 days produced significantly higher mean intragastric pH values when compared with lansoprazole 30 mg once daily, with mean total 24-hour intragastric pH values that were greater then 4.5 versus 4.13 for lansoprazole 30 mg (P<.01; for all doses). The percentage time that the intragastric pH was greater than 4 was also
significantly longer with TAK-390MR when compared with lansoprazole. In a study of 4092 patients who were negative for *Helicobacter pylori* and who had EE (LA grades A-D), TAK-390MR demonstrated a significantly higher overall healing rate at 60 mg and 90 mg when compared with lansoprazole 30 mg once daily (92.7% and 93.6% versus 88.9%, respectively). TAK-390MR 90 mg was also significantly superior to lansoprazole in healing grades C and D EE by week 8 (88.9% versus 81.5%). TAK-390MR in a dose of 30 and 60 mg once daily was significantly superior to placebo at maintaining EE healing over 6 months as well as relieving heartburn. Most patients receiving TAK-390MR were heartburn free for over 90% of treatment days.

**NEW ACID SUPPRESSION TREATMENTS**

Despite a choice of treatments for GERD, a substantial proportion of patients continue to be inadequately treated and experience persistent symptoms or develop complications. Furthermore, complete resolution of reflux symptoms does not guarantee normalization of intraesophageal and intragastric pH, because 50% of GERD patients without BE continue to show pathologic GERD and a low intragastric pH despite PPI therapy that achieves complete control of reflux symptoms. New strategies are needed to achieve better acid suppression in such refractory patients.

Tenatoprazole is a new imidazopyridine-based PPI with a prolonged plasma half-life (9.3 hours) when compared with currently available PPIs (1–2 hours). The stability of inhibition and the long plasma half-life of tenatoprazole should result in prolonged inhibition of acid secretion when compared with omeprazole. Studies in volunteers have shown that tenatoprazole 40 mg daily produces similar acid suppression to esomeprazole 40 mg during the daytime but is more effective during the nocturnal period with a significantly greater increase in intragastric pH for the overall 24-hour period. During the nocturnal period on tenatoprazole, the mean pH was 4.64 versus 3.61 and the mean percentage of time with a pH greater than 4 was 67.2% versus 45.9%, respectively. Our meta-analysis indicates that 24-hour and nighttime acid suppression with S-tenatoprazole-Na (STU-Na) 60 mg omni mane is more effective than the most potent PPI, esomeprazole at a standard dose. The effect of tenatoprazole was still present during the nighttime period 5 days after treatment withdrawal and was attributed to the significantly longer $t_{1/2}$ and increased area under the curve of tenatoprazole when compared with esomeprazole. Nocturnal acidity and NAB was also decreased with significantly shorter durations.

AGN 201,904-Z is a newly developed acid-stable prodrug of omeprazole that provides continued metered absorption. AGN 201,904-Z 600 mg when compared with esomeprazole 40 mg in volunteers showed a median 24-hour pH and percentage time of pH of 4 or greater that was significantly higher at day 5 (5.6 versus 4.5 and 87% versus 57%, respectively; $P < .0001$). Moreover, the difference was significant at day 1 and day 5 for median pH (for day 5, 5.4 versus 3.0, respectively) and for the percentage time with a pH of 4 or greater for the nocturnal period. The percentage of time the pH was 4 or greater during the nocturnal period was more than twofold greater for AGN 201,904-Z when compared with esomeprazole after 5 days of dosing (83% versus 38%, $P < .0001$). These data suggest that AGN might provide better clinical efficacy with the once daily dosing when compared with current PPIs for the management of GERD that fails to respond completely to conventional PPI therapy.

**POTASSIUM-COMPETITIVE ACID BLOCKERS**

This new class of acid pump inhibitors competes with the potassium channel of the H+ K+ ATPase, a concept first introduced in studies of SCH28080 in 1982. AZD0865 is
a member of this class of acid inhibitory drugs. In vitro studies have shown a more rapid onset of action and greater potency when compared with PPIs. The onset of action, in time to reach a pH greater than 4 lasting for at least 30 minutes during the initial 4 hours after dosing, was dose dependent and ranged from 73 to 41 minutes, respectively, on day 1.

Two randomized clinical trials of AZD0865 failed to show a significant difference when compared with esomeprazole in healing EE or treating NERD; however, these trials were performed with once daily doses of AZD0865, which, on the basis of pharmacokinetic data, would require more than once daily dosing to maintain the rapidly elevated pH seen in the pharmacodynamic studies. The question of whether this new class drug could provide a clinical benefit has not been appropriately answered.

NEW DIRECTIONS FOR TREATMENT

GABA-B Agonist Baclofen

It has been suggested that the best studied “medical therapy” for consideration in patients with non-acid reflux may be the γ-aminobutyric acid (GABA-B) agonist baclofen. Several studies have shown that baclofen reduces acid reflux and significantly improves duodenogastric reflux and associated reflux symptoms that persist during PPI therapy. It also reduces postprandial acid and non-acid reflux and their associated symptoms by decreasing the number of transient lower esophageal sphincter relaxations. XP19986 is an investigational prodrug of R-baclofen. A recent study enrolled 50 GERD patients who were given XP19986 in escalating single doses of 10, 20, 40, and 60 mg following a high-fat meal. A significant reduction in total reflux episodes over the 12-hour monitoring period after dosing with XP19986 when compared with placebo was observed for the combined dose groups (P = .005), with the 40 and 60 mg doses being the most effective. Nevertheless, few long-term efficacy or safety data for this drug are available. A GABA-B agonist by controlling transient lower esophageal sphincter relaxations may provide an alternate approach for the treatment of GERD during PPI therapy or when reflux symptoms remain refractory to PPI use, and studies in long-term therapy are needed.

5-HT4-Receptor Agonists

Tegaserod is a partial 5-HT4-receptor agonist acting throughout the gastrointestinal tract that acts as a prokinetic and sensitivity modulator. It has recently been withdrawn from the market. Tegaserod 6 mg twice daily for 2 weeks significantly decreased the frequency of occurrence of heartburn/acid reflux and regurgitation. Moreover, tegaserod 1 mg per day caused a significant decrease in postprandial esophageal acid exposure in GERD patients. Nevertheless, similar numbers of acid and non-acid reflux episodes for placebo and tegaserod were observed in healthy subjects. Further studies are needed to confirm the efficacy of other 5-HT4 agonists in the treatment of GERD.

SUMMARY

Good evidence suggests that antisecretory therapies that raise intragastric pH to 4.0 or greater for the longest duration provide the best symptom relief and healing of esophageal mucosal damage; however, a poor response is increasingly recognized and largely due to the fact that currently used PPIs are short acting. Continuous maintenance therapy is also effective to reduce the likelihood of the recurrence of esophagitis and to control symptoms in the long term.
PPIs given once daily and twice daily are effective approaches to heal esophagitis and control symptoms, although PPI failure or PPI-refractory GERD is an increasing reason for referral to a gastroenterologist. Both acid and non-acid reflux should be considered when a patient presents with PPI failure. In such PPI-refractory cases, an accurate diagnosis should be established before further treatment. Despite the recognized success of medical treatment with PPIs, there are several important unmet clinical needs, including nocturnal symptoms, sleep disturbance, OSAS, NERD, and supraesophageal syndromes. IR-OME, TAK-390MR, and the new PPIs offer flexibility in dosing and potentially improved nocturnal pH control, particularly early in the nighttime period when most reflux occurs. Surgical treatment is a useful option for patients who are refractory to PPIs and in whom persistent reflux has been confirmed; however, long-term antireflux medication is still frequently needed after surgical treatment. Alternative approaches in the future might be to control transient lower esophageal sphincter relaxations with drugs such as the GABA-B agonists or improved, predictable, and prolonged acid suppression with one of the new generation long-acting acid suppressants.

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