ABSTRACT

Gastroesophageal reflux disease (GERD) affects approximately 20% of the US population and is one of the most common acid-related disorders in US adults. One of the key symptoms of this often chronic disorder is heartburn. Gastroesophageal reflux disease is known to cause heartburn, and the presence of acid in the esophagus for prolonged periods is now known to place patients at risk for serious sequelae, such as Barrett’s esophagus and esophageal cancer. Therefore, long-term management options are needed, including lifestyle changes, pharmacological therapy, surgery, and endoscopic intervention. Proton pump inhibitors have been found to be superior to other medications both in inducing symptom resolution and healing esophagitis. The outcomes reported from surgical and endoscopic treatments are mixed. Recent data suggest that approximately one fourth of surgically treated patients will require continued antisecretory therapy for persistent GERD symptoms postoperation. Though a number of endoscopic procedures have been approved for use in the United States, their effectiveness and their roles in clinical practice remain controversial. (Adv Stud Med. 2003;3(3A):S123-S127)

MEDICAL THERAPY FOR HEARTBURN

HISTAMINE-TYPE 2 RECEPTOR ANTAGONISTS VERSUS PROTON PUMP INHIBITORS

There are 2 main classes of drugs available today that are used in the long-term treatment of GERD in adults: histamine type-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). However, evidence clearly indicates that of the two, PPIs should be the mainstay of medical therapy for most patients. In a large community-based trial conducted by Howden et al, 593 individuals with symptomatic GERD were randomized to receive either an initial dose of the H2RA, ranitidine, or the PPI, lansoprazole. Four therapeutic strategies were compared in which some subjects remained on a constant dose of ranitidine 150 mg bid or lansoprazole 30 mg qd for 20 weeks, while others began initially on either ranitidine 150 mg bid or lansoprazole 30 mg qd and then were switched to the other medication. Subjects were asked to keep diaries of their symptoms, specifically to log the severity of their daytime and nighttime heartburn as well as...
the percentage of 24-hour heartburn-free days. Results indicated that regardless of whether a trial participant was given the PPI first or second, the individual experienced significantly greater heartburn relief and relief of other reflux-related symptoms when treated with a PPI. For example, the lansoprazole group had a significantly higher percentage of 24-hour heartburn-free days (median 81.4%; \( P < .01 \)) than other groups (66.6%, 66.9%, and 73.6%, respectively).2

**A Comparison of PPIs**

Castell et al studied a large number of patients with GERD who were randomized to receive either lansoprazole 30 mg qd or esomeprazole 40 mg qd. After 4 weeks of treatment, patients in both groups experienced heartburn-free days for approximately 70% of the study period. For both lansoprazole and esomeprazole, relief of nighttime symptoms occurred after 1 day; daytime symptom resolution was achieved in 2 days. Both medications were capable of completely resolving heartburn symptoms among study participants after 4 weeks of therapy approximately 60% of the time.3 A similar study recently completed by Howden et al compared the effectiveness of lansoprazole and esomeprazole in patients with heartburn and erosive esophagitis and found no statistically significant difference between the 2 drugs at either day 1 or week 1 of therapy.4

**Medical Therapy for Healing Esophagitis**

While heartburn is the hallmark symptom of GERD, results of North American studies indicate that 40% to 60% of patients with GERD have evidence of esophagitis at endoscopy. Evidence shows a causal relationship between GERD and Barrett's esophagus as well as an increased risk of esophageal adenocarcinoma from Barrett's.5 Thus, prompt resolution of heartburn as well as healing of esophagitis should be the long-term goals in individuals with GERD. Richter and investigators compared lansoprazole and omeprazole to placebo in a randomized, double-blind, multicenter study of 3510 patients with erosive esophagitis diagnosed via endoscopy. Their data indicate that PPIs are statistically significantly better than placebo in healing erosive GERD, and that lansoprazole 30 mg qd relieved heartburn faster and more effectively than omeprazole 20 mg qd. Eighty-one percent of patients receiving lansoprazole were healed of erosive esophagitis by week 4 compared with only 33% of those randomized to placebo. By week 8, 95% of patients treated with lansoprazole were healed compared with 53% of patients receiving placebo.4 These data further support the studies by Castell and Howden that showed that both lansoprazole and esomeprazole achieve excellent rates of healing in patients with GERD after both 4 and 8 weeks of treatment.3,4

**Medical Therapy for Maintaining Remission**

What about maintenance of healing and symptom-free remission? In clinical practice, PPIs and H2RAs are most frequently prescribed for sufferers of GERD. Proton pump inhibitors have consistently been deemed superior to H2RAs. In a study published by Gough et al in 1996, data indicate that even a high dose of ranitidine (300 mg bid) is inferior to the PPI, lansoprazole (30 mg qd or 15 mg qd) in maintaining remission of symptoms. This may be due in part to the fact that patients with chronic GERD who take H2RAs frequently develop tolerance to these medications—a phenomenon that so far has not been found to occur with PPI use.7 When pH-related endpoints (either intragastric pH or intraesophageal acid exposure) were examined in a trial performed in 23 individuals with GERD who were treated with the PPI, omeprazole 20 mg/day, there were no significant differences in those measurements at 3 or 6 months. This suggests that patients do not develop a tolerance to PPIs.8

**Safety of Long-term PPI Treatment**

Long-term use of PPIs appears to be both effective and safe. The incidence and spectrum of adverse events associated with the use of PPIs is very similar to that associated with H2RAs. Both classes of drugs are considered to be very safe. In the 16 years since physicians began prescribing PPIs worldwide there has been no evidence to indicate that long-term exposure to PPIs causes the development of gastric carcinoids, atrophic gastritis, intestinal metaplasia, or gastric adenocarcinoma. Furthermore, since no cases of clinically significant B12 deficiency have been associated with PPI therapy, it is not necessary to monitor B12 levels in routine practice (Table 1).9-11

Because pregnant women frequently suffer with GERD, a review of 5 cohort studies was conducted by Nikfar et al to examine the safety of PPI use during
pregnancy. In approximately 600 pregnancies exposed to PPI therapy during the first trimester, the relative risk of a major malformation was 1.18 (95% confidence interval). Thus, this study found that PPIs present no major teratogenic risk when used in the first trimester of pregnancy.12 The majority of PPIs are Category B, according to the Food and Drug Administration, although omeprazole is rated as Category C.

**Surgical Intervention**

Surgery is another management option for the treatment of GERD. However, several factors must be taken into consideration before proceeding with surgery. The first is to evaluate the nature of an individual's symptoms. It is vital to understand that a patient presenting with typical reflux-related symptoms is much more likely to do well with surgical therapy than one with atypical symptoms. Heartburn sufferers, for example, are more likely to experience better outcomes with fundoplication than individuals whose primary symptom is cough, hoarseness, or asthma. Furthermore, individuals who respond well to medical therapy have a better chance for success with surgery than those who do not. Likewise, individuals with erosive esophagitis are more likely to experience a good outcome with surgery than those with nonerosive disease. Data from Fenton et al reported that heartburn resolved in 91% of patients with erosive esophagitis versus 56% of patients with negative endoscopies. Likewise, 94% of patients who underwent laparoscopic fundoplication for erosive esophagitis reported being satisfied with the outcome of the surgery as compared with 79% who did not have esophagitis confirmed on diagnostic testing.13

Thus, it is critical that careful preoperative diagnostic testing be performed to confirm that GERD is the cause of symptoms. Some patients with suspected symptoms of GERD, particularly those with atypical symptoms or nonerosive disease, may actually be suffering from a disease other than GERD. The symptoms of GERD certainly can be misleading and may overlap those of other conditions. Ambulatory esophageal pH monitoring helps to confirm the diagnosis of acid reflux and establishes a link between acid reflux and symptoms. Therefore, an appropriate preoperative evaluation can help to avoid the performance of unnecessary surgical procedures.

Patients' preferences must also be taken into account when deciding whether to manage GERD via surgical therapy. A younger patient who does not want to commit to a lifetime of medication or who has difficulty complying with pharmacotherapy is an ideal surgical candidate. For each patient, it is very important to assess the likelihood of a successful outcome following surgical antireflux therapy. The key criteria to allow the risk stratification of potential candidates for surgical antireflux therapy are stated in Table 2.

### Table 1. Safety of Long-term PPI Treatment

- Incidence and spectrum of adverse events similar to H2RAs
- 16 years of worldwide experience and over 219 million treatments
- No evidence that long-term PPI treatment promotes development of:
  - gastric carcinoids
  - atrophic gastritis
  - intestinal metaplasia
  - gastric adenocarcinoma
- No need to monitor B12 levels in routine practice

PPI = proton pump inhibitor; H2RA = histamine type-2 receptor antagonist. Data adapted from references 9, 10, 11.

### Table 2. Criteria for Surgery

- Good surgical candidate
- Trained, experienced surgeon
- Confirmed diagnosis of GERD
- Demonstrated response to PPI (failure to respond to PPI predicts poor response to surgery)

GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.
In addition, it is important to take into consideration the potential risks associated with surgical anti-reflux therapy. According to a study published in The Journal of Gastrointestinal Surgery in 2001, a number of adverse events may be associated with surgery. Bammer and investigators examined the 5- to 8-year outcomes of the first laparoscopic Nissen fundoplications performed compared with traditional open abdominal surgery. Of 171 patients who underwent laparoscopic surgery and could be followed for at least 5 years, 96.5% reported continued satisfaction with the outcome of the procedure. This was comparable to open surgical procedures. However, these patients did report some persistent symptoms, including 28% reporting dysphagia. Bloating occurred in 21% of patients postoperatively. Seven percent of patients in this study required dilatation and 14% required continued PPI use in spite of surgical treatment.\(^{14}\)

Whereas the prior study examined cases performed in a tertiary care center known for their expertise in gastrointestinal procedures, Vakil conducted a similar outcomes study, but in patients whose procedures were performed in community-based centers. Eighty-three GERD patients were interviewed approximately 2 years after their surgical anti-reflux procedures. The reasons they provided for opting for surgery included inadequate symptomatic relief with medical therapy (46%), hope for a cure (26%), fear of long-term PPI effects (17%), and cancer prevention (10%). These findings were quite interesting in that those unresponsive to medical therapy are less likely to improve with surgery. In addition, no adverse effects have been attributed to long-term PPI use. Finally, there is no convincing evidence to suggest that surgery decreases the likelihood of developing esophageal cancer. Fifty-eight percent of patients reported overall satisfaction; 29% of patients were somewhat satisfied and 13% of patients were dissatisfied. Sixty-seven percent of patients presented with new dysphagia, bloating, and gas. Twenty-seven percent of patients were still taking drugs for GERD at follow-up. Furthermore, 8% of patients had dilatation and approximately another 8% underwent repeat surgery.\(^{15}\)

This fairly high incidence of side effects and the need for repeat procedures leaves open the question as to whether an alternative therapy to medication or surgery might prove more successful. Let us consider endoscopic management of GERD.

### Endoscopic Therapy

There are a number of endoscopic therapies currently under evaluation for the treatment of GERD. The 2 on which we will focus are the Stretta and Endocinch procedures. The Stretta procedure involves the delivery of radio frequency energy to the lower esophageal sphincter to create thermal lesions below the mucosa at the gastroesophageal junction.\(^{16}\) With Endocinch treatment, sutures or plications are placed in the area of the lower esophageal sphincter to create a reflux barrier.\(^{17}\)

The findings reported by Triadafilopoulos et al of an open trial performed on 118 patients with symptoms of GERD but with either no esophagitis or Grade I or II esophagitis indicate that patients with nonerosive conditions or with mild esophagitis experienced improvements in GERD-related health and quality of life after the Stretta procedure. In addition, there were some improvements in certain domains of the 36-item Short Form Health Survey, a validated general survey instrument used to assess quality of life. However, at 6 months after the Stretta procedure was performed, 23% of patients still had esophagitis; 12 months post-Stretta, 34% of patients were still using PPIs for their GERD-related symptoms.\(^{16}\)

By comparison, when endoscopic plication was studied in a multicenter trial of 64 patients with mild

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<th>Table 3. Complications of Endoscopic Therapies for GERD</th>
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GERD = gastroesophageal reflux disease; ELGP = endoluminal gastroplasty. Data adapted from references 16, 17.
GERD requiring PPIs, but who either had no esophagitis or mild esophagitis, the results of this study were similar to those reported with the Stretta procedure. Data reported after 6 months showed improved symptoms and 24-hour pH-metry scores. However, in this trial, 11 patients required repeat surgery, and one third of patients experienced pharyngitis. Others developed a myriad of complications including vomiting, abdominal pain, chest pain, and 1 patient reported 2 cases of bleeding from suture perforation. It is important to note that as many as one third of the patients in this study needed to restart acid suppressive therapy, mostly with PPIs.\(^{17}\)

In summary, only data from small, uncontrolled trials in patients with nonerosive disease or mild esophagitis are available for the endoscopic methods of treating GERD. A number of complications ranging from fever and chest/abdominal pain to bleeding and even aspiration and death have been reported (Table 3).\(^{18}\) Some of these complications are undoubtedly related to the learning curve for endoscopists performing these procedures that affects patient outcomes. Thus, the use of endoscopic therapies should be confined to clinical trials at centers with an appropriate level of expertise. In so doing, we can be confident that our patients' best interests are being served.

**Conclusion**

Long-term PPI treatment has been proven safe and effective for GERD patients. Surgery should be considered only after a positive diagnosis of GERD has been established and after carefully considering the risk-benefit ratio in the individual patient. It should be noted that many GERD sufferers still require medication postoperatively. Endoscopic treatment still has not been adequately studied and, therefore, its application in medical practice today may be premature.

**References**

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