

## Lifestyle Modifications and the Control of GERD Symptoms

The following are highlights from roundtable discussions that took place on October 17, 1999, in Phoenix, Arizona, during a symposium on the management of gastroesophageal reflux disease.

**Dr. DeVault:** Patients are becoming more sophisticated. They often consult their primary care physician after having self-treated with antacids, over-the-counter H<sub>2</sub>RAs [histamine<sub>2</sub> receptor antagonists], and lifestyle modifications. So treatment algorithms that include these means as a form of initial therapy may not be very applicable among an educated population.

**Dr. Webb:** Lifestyle modifications should be encouraged no matter what agents the patients receive. A parallel logic is if we prescribe an agent to lower a patient's cholesterol level, we would still recommend a low-fat diet.

**Dr. DeVault:** There is very little difference between GERD [gastroesophageal reflux disease] patients who have undergone lifestyle modifications and those who did not. The objectives of lifestyle modifications are laudable and should be emphasized but to assume that they are going to help the majority of GERD patients is probably naive.

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**Dr. Webb:** I agree.

**Dr. Wolfe:** Some people may actually regard a recommendation for lifestyle modifications as punitive, so physicians should be careful not to imply that GERD is self-induced. Although GERD can be exacerbated by certain

lifestyles, it is a disease with real pathophysiology.

There are, however, 2 painless lifestyle modifications we should urge our patients to try. The first is to use a 6-inch foam wedge to elevate the thorax and the head while sleeping. The other is to chew gum. The chewing motion has been shown to increase salivary flow and the concentration of bicarbonate saliva.

### Administration of PPIs

**Dr. Wolfe:** An important issue regarding the use of PPIs [proton pump inhibitors] is the timing of administration. It is commonly known that the presence of food in the stomach decreases the absorption of lansoprazole. But to assume that a meal does not affect the activities of the other PPIs is not exactly correct. Although food does not significantly diminish the absorption of the other PPIs, it does affect the activities of these drugs. PPIs inhibit stimulated proton pumps, and all PPIs should thus be given before breakfast for maximal benefit. The importance of the time of dosing should be made clear to the patients, especially because many take PPIs before going to bed as they would do with an H<sub>2</sub>RA. Although H<sub>2</sub>RAs are clinically effective when taken before bedtime, PPIs are not.

Any discussions of off-label uses are identified by an asterisk within the text.

Another important point is that H<sub>2</sub>RAs should not be coadministered with PPIs. H<sub>2</sub>RAs decrease the activity of the gastric proton pump. Since PPIs act by blocking active proton pumps, a coadministered H<sub>2</sub>RA can severely decrease the acid-suppressive effect of a PPI.

**Dr. DeVault:** From a managed care perspective, educating the pharmacy staff regarding the proper use of PPIs is very important. The availability of H<sub>2</sub>RAs over the counter has further complicated this issue because patients undergoing PPI therapy may use H<sub>2</sub>RAs for breakthrough symptoms. As a result, GERD symptoms may worsen, and sometimes these patients are diagnosed with refractory reflux. \*Rather than taking H<sub>2</sub>RAs to control breakthrough symptoms, a double dose of PPI should be considered in severe cases of GERD.

### Prokinetic Agents

**Dr. Webb:** I am often asked whether a clinician should prescribe a prokinetic agent for a patient who is experiencing breakthrough symptoms with PPI treatment. I am interested in hearing your views on this subject.

**Dr. DeVault:** I generally do not add a different class of agent in the treatment of GERD patients until I know that the class of drug that the patient is currently taking has been optimally utilized. \*If the patient was taking a PPI once a day, I'd be more likely to recommend a twice-a-day regimen (before breakfast and before dinner) before I would add another drug of a different class. Besides, it is more cost effective to use 2 doses of PPI per day rather than a single dose of PPI and a prokinetic agent. Both regimens cost about the same, but 2 daily doses of a PPI are more effective in acid suppression.

**Dr. Wolfe:** Currently, 2 prokinetic agents are available in the United States, metoclopramide and cisapride.\* Both drugs have considerable side-effect profiles. Cases of tardive dyskinesia have been documented for patients taking metoclopramide. The use of cisapride is uncommonly associated with cardiac arrhythmias.

**Dr. DeVault:** If cisapride is to have an effect on GERD, it is likely that the dosage requirement will be 20 mg 4 times a day. I can't expect any of our patients to take cisapride 4 times a day. That is as likely as having them take antacids 8 times a day to heal an ulcer. Taking cisapride 4 times a day is also not very cost effective.

### Cost Effectiveness of PPI Therapy

**Dr. Wolfe:** If cost were not an issue, there would be no need for a debate about which acid-suppression therapy to use. The PPIs are clearly more effective than the H<sub>2</sub>RAs in the treatment of GERD requiring daily therapy. The most cost-effective therapy is one that works.

**Dr. Webb:** Considering the various complications associated with GERD, especially the development of Barrett's esophagus and esophageal adenocarcinoma, I think our goal should be the complete elimination of GERD symptoms. As PPIs become increasingly cost effective, we will see more PPI usage.

### PPIs and Gastrospecificity

**Dr. Ashby:** Proton pumps exist in other organs in addition to the stomach. It has been suggested that PPI side effects are related to their actions on nongastric proton pumps. Do you

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\*Since this meeting was held, cisapride has been taken off the market in the United States.

know of any difference in side-effect profiles relating to the gastrospecificity of the PPIs?

**Dr. Webb:** There seems to be a high incidence of diarrhea associated with the use of lansoprazole. This is probably due to the lack of tissue-specific activity of lansoprazole. Diarrhea is one of the most limiting side effects associated with the use of this PPI in my experience.

### Safety

**Dr. Wolfe:** The most important principle in the treatment of any disease is to weigh the risks of treatment versus the benefits. The risk of PPI use is primarily theoretical because despite observed increases in serum gastrin level, hyperplasia has not been observed in human subjects. On the other hand, GERD is a risky disease. Long-standing GERD can lead to serious complications. So any theoretical risk associated with PPI use is entirely offset by the benefits patients derive from the treatment of GERD.

### Barrett's Esophagus

**Dr. Ashby:** Do you believe that a patient who has mild esophagitis is at risk for Barrett's esophagus in the future? Furthermore, does treatment change the outcome?

**Dr. Webb:** Presently, there are no definitive data that show that treatment of GERD will prevent the development of complications such as Barrett's esophagus. Currently, the consensus among clinical studies is that there is a statistical association between the occurrence of GERD and the development of Barrett's esophagus and esophageal adenocarcinoma. Therefore, we have to treat GERD with the belief that it will prevent the development of more disease.

**Dr. Wolfe:** I agree that it is faith at this point. We have to treat GERD with the belief that the treatment will prevent the progression from esophagitis to Barrett's esophagus, dysplasia, and invasive cancer.

### Pantoprazole Intravenous Formulation

**Dr. Wolfe:** The biggest development in the use of PPIs is the impending availability of an IV [intravenous] formulation of pantoprazole. An IV PPI may be very valuable especially in the intensive care setting. Certainly the onset of action for an IV formulation will be more rapid than an oral PPI suspension, which to date have not been proven clinically effective.

**Dr. Webb:** It is important for GERD patients to continue their PPI therapy even when they are in an intensive care setting. Acid rebound may be an issue if the medication is discontinued.

**Dr. DeVault:** Tachyphylaxis to H<sub>2</sub>RA is also an important issue in an intensive care setting. H<sub>2</sub>RAs begin to lose their efficacy in critically ill patients at about the same time these patients really get sick (the third day after a trauma, burn, or major surgery). With IV PPI, these patients can obtain maximal acid suppression without the worry of tachyphylaxis.

### Dose Response

**Dr. Webb:** Most of the PPIs show a consistent dose-response curve. The exception, however, is lansoprazole. In a set of studies presented in the prescribing information of lansoprazole, the antisecretory effect of a 15-mg dose resulted in a higher percentage of healing in patients with erosive esophagitis than a 30-mg dose.

**Dr. DeVault:** In the use of ranitidine,

an H<sub>2</sub>RA, increasing the dosage from 150 mg bid to 300 mg bid can add a marginal increase in response rate, but the efficacy does not approach that of 20 mg of omeprazole or 40 mg of pantoprazole once a day.

**Dr. Wolfe:** Increasing the dosage of an H<sub>2</sub>RA also results in a quicker tachyphylaxis response.

### Prevalence of Acid-Peptic Disease and the Need for Acid-Suppression Therapy

**Dr. DeVault:** The impact of acid-suppression therapy on formulary cost is primarily due to the prevalence of acid-peptic disease and the need for patients to be treated. There are definitely drugs that are more expensive than PPIs, however, because these drugs are used to treat diseases that are less common than acid-peptic disease, their impact on formulary cost is less than that of acid-suppression therapies.

**Dr. Wolfe:** The prevalence of acid-peptic disease has often been underestimated partially because it is sometimes equated with peptic ulcer. In fact, the most common acid-peptic disease, by far, is acid reflux.

### “Step-Up” Therapy in the Treatment of Erosive Disease

**Dr. DeVault:** The problem with step-up therapy is that it is very time consuming. In some cases, it can take several months. Another problem with step-up therapy comes from the fact that many treatment guidelines propose a step-down therapy once the initial erosive disease has been healed. If an H<sub>2</sub>RA has already failed in a step-up strategy, then it is not likely to work as part of a step-down strategy for the prevention of future disease.

**Dr. Ashby:** I agree. Patients who have failed high-dose H<sub>2</sub>RA therapy are not likely to respond to H<sub>2</sub>RA in a step-down therapy. My experience is that a step-down strategy to prevent disease recurrence is very difficult.

**Dr. Wolfe:** I think we all agree that for most patients, the therapy used to control GERD symptoms and heal mucosal disease should generally be the same one used in maintenance therapy.

### Severity of Esophagitis and the Relapse of Disease

**Dr. Wolfe:** Are there any studies that suggest a correlation between the grade of esophagitis and the likelihood of disease recurrence once the original injury has been healed?

**Dr. Ashby:** There is the perception that patients with erosive esophagitis grades 3 and 4 will be more likely to relapse than those with esophagitis grades 1 and 2. It is probably true that as many as 10% to 30% of patients may not experience a recurrence of disease even without maintenance therapy. However, there isn't a method to determine who will and who will not develop erosive disease again when acid-suppression therapy is withdrawn.

### The Role of Endoscopy

**Dr. Ashby:** The role of endoscopy in assessing the status of maintenance therapy for patients with healed esophagitis is an evolving one. It is very difficult to determine which patients will benefit from endoscopy.

**Dr. DeVault:** To recommend endoscopy for all GERD patients is a simplistic and unrealistic approach. A feasible approach is to recommend endoscopy for patients whose symp-

toms recur.

Certainly, there is also a risk versus benefits issue. A 22-year-old woman with 5 years of reflux will have a very low risk for developing Barrett's esophagus. In fact, the risk of disease in this patient may approach the risk of the endoscopy procedure itself. But, the risk of disease in a 50-year-old man with 20 years of reflux is another matter.

**Dr. Wolfe:** I agree that the chance of a young woman having Barrett's esophagus is very slim, however, the risk of missing Barrett's is clearly far greater than risks associated with endoscopy. Much of the data we have on the safety of endoscopy is based on old literature. Endoscopy is now a very safe procedure, and in a person who is otherwise healthy, there is virtually no risk.

It is not known whether endoscopy makes a difference in preventing the development of Barrett's esophagus and esophageal adenocarcinoma. However, based on available data, most gastroenterologists believe that untreated esophagitis will lead to those serious complications.

### Onset of Action

**Dr. Wolfe:** The onset of action of PPIs is used as a marketing tool when in reality all PPIs are delayed with regard to their onset of action. \*I routinely advise my GERD patients to take their PPI twice a day for the first 3 days of therapy. In my experience, this practice results in symptom relief during the first day in virtually all GERD patients.

### Atypical GERD Presentation

**Dr. Webb:** We are finding that it takes a higher dose of a PPI to effectively treat extraesophageal manifestations of GERD. Has that been your experience?

**Dr. Wolfe:** Yes. Generally, in medical literature, extraesophageal symptoms of GERD, such as acid laryngitis, chest pain, and asthma, are treated with 2 doses of PPI, once before breakfast and once before dinner.

A study published by Harding et al in 1996 indicated that many asthma patients with GERD (approximately 27% in this study) require a greater than 20-mg per day dose of omeprazole to control acid reflux. This study also showed that omeprazole improved asthma symptoms by more than 20% and improved pulmonary function in 73% of asthmatics with GERD after 3 months of acid-suppression therapy. This study strongly suggests a role of acid reflux in respiratory disease.

This paper was criticized because only a small subset of patients accounted for nearly all of the improvements. However, this is exactly the point. GERD is only a cause in a subset of asthma cases. The biggest challenge now is to be able to identify the individuals who belong to this subset.

The problem with laryngitis, cough, and asthma is that we really don't know how much reflux is required to cause these symptoms. Does a 2% distal and 0.5% proximal acid exposure in dual channel pH probe monitoring have any significance? These results are by definition negative. But could a 0.5% exposure to acid reflux (7.2 minutes a day) be a cause for oropharyngeal/respiratory problems?

In my experience, pH tests did not rule out acid reflux as a cause of these problems except in very rare cases. Therefore, it seems to be more reasonable to proceed with a therapeutic trial and delay the pH test until later on.

There are 2 major indications for the use of pH probes. One is for repeated chest pains, and the other is for the assessment of the adequacy of GERD therapy.

**Dr. DeVault:** Patients with atypical symptoms should not undergo surgery because of a positive response to a therapeutic trial. Surgery should be undertaken with more concrete evidence of GERD such as the presence of erosive disease, Barrett's esophagus, or an abnormal result on a pH test. If you know that a patient wants a surgical opinion, a pH test early in the course of decision making can be quite helpful.

### Surgery

**Dr. Wolfe:** Generally, patients who do not respond to medical treatment will not respond to surgery. In cases of nonresponse to GERD treatment, etiologies other than GERD should be considered.

**Dr. DeVault:** We must also be careful about atypical esophagitis due to eosinophilic disease, Crohn's disease, et cetera. There is certainly a role for biopsy in these cases.

Conversion from a laparoscopic surgery to an open procedure occurs in approximately 6% of patients because of difficulty with exposure, dissection, or even equipment failure in some cases.

A study by Deschamps et al<sup>2</sup> clearly showed the importance of a learning curve in laparoscopic fundoplication. In this study, patients who received antireflux surgery in 1996 at the Mayo Clinic were divided into 2 groups based on the timing of their procedure. It was observed that the patients of the first group, who underwent surgery earlier in the year, experienced significantly longer operative time and hospitalization than subsequent patients (248 versus 240 minutes and 2 days versus 1 day, respectively). A higher percentage of patients in the first group also required laparotomy (23.3% versus 6.7%).

We found that 20% of our patients who underwent antireflux received

PPI therapy 5 years after their procedure. They went back on PPI therapy for many reasons. However, nearly a third of those patients went back clearly as a result of experiencing reflux symptoms.

**Dr. Wolfe:** A problem with fundoplication is that it makes it quite challenging to biopsy the lower esophagus, which is normally the toughest place to biopsy accurately. For a patient with Barrett's esophagus, it becomes extremely difficult.

**Dr. Webb:** Some surgeons have indicated to me that their patients sometimes have the expectation that surgery is going to reverse their Barrett's esophagus. Of course, this expectation is unrealistic. However, many surgeons also believe that surgery is a better treatment option than medical therapy. I am not convinced of that. I don't think there has ever been a really good head-to-head comparative trial of the 2 options.

### Surveillance Biopsy

**Dr. Wolfe:** What are your opinions on surgery and Barrett's esophagus? Data obtained 15 years ago suggested that surgery could reverse metaplasia. I don't think anyone believes that anymore.

**Dr. DeVault:** The point is that the rate of cancer development in patients who undergo medical management versus those who undergo surgery is the same. There have been a few cases where a patient receives surgery only to present a year later with dysphagia induced by a developing tumor in the distal esophagus.

**Dr. Webb:** Surveillance biopsy is critical for surgery patients, particularly if the patient has low-grade dysplasia. It is technically quite challenging, but it can be done.

**Dr. DeVault:** Barrett's surveillance after surgery is necessary but labor intensive. Maybe we should be doing more staining to better target our biopsies.

#### Manometry

**Dr. Webb:** I can not overemphasize the importance of knowing that a patient has adequate peristalsis prior to antireflux surgery.

**Dr. Wolfe:** Manometry is indispensable for a patient scheduled to undergo surgery. For a person with poor peristalsis, surgery converts them from a GERD patient into a patient with iatrogenic achalasia. It is totally unacceptable to recommend fundoplication to a patient with hyperperistalsis or aperistalsis.

#### Esophageal Strictures

**Dr. DeVault:** The best data available indicate that continuing acid-suppres-

sion therapy decreases the rate of stricture recurrence once the initial symptoms have been controlled.

**Dr. Wolfe:** There are data that show that PPI therapy increases the length of time between dilations and prevents the recurrence of strictures. When perforations and other endoscopy-related complications occur, they usually occur with dilation. The risk of a PPI is minimal, but the benefits are remarkable.

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