A Supplement to
Family Practice News®

Highlights of a Symposium

Managing Acid-Related Disorders Through the Ages of Mankind

Held October 22, 2002, in Seattle, Wash.

Introduction

A message from A. Mark Fendrick, MD, Associate Professor of Internal Medicine, Health Management and Policy, University of Michigan Medical Center, Ann Arbor, who moderated the live symposium on which this supplement was based.

At an educational satellite symposium held in Seattle in October 2002, three authorities on the subject of acid-related disorders provided a concise but informative overview of the evolution of the disorders across the age spectrum, from children to the elderly.

The faculty reviewed the latest data pertaining to the use of antisecretory therapy for children, particularly the use of proton pump inhibitors (PPIs) for refractory symptoms. The speakers also assessed the pros and cons of the available long-term medical, endoscopic, and surgical options for adult patients with chronic gastroesophageal reflux disease. Finally, the panel evaluated the available treatment strategies to reduce the risk of gastrointestinal adverse effects for individuals who require nonsteroidal antiinflammatory drugs (NSAIDs). The presence of risk factors for NSAID gastrointestinal (GI) complications and the use of low-dose aspirin for cardioprevention were deemed critical determinants in deciding when cyclooxygenase-2 selective inhibitors and/or PPIs should be used to reduce the risk of NSAID-related GI complications.

Primary care physicians whose patient populations encompass the spectrum of acid-related disorders will find the information relevant and readily applicable to their clinical practice.

A. Mark Fendrick, MD

GERD Often Overlooked in Pediatric Patients

According to a Boston pediatric gastroenterologist, gastroesophageal reflux disease (GERD), when undiagnosed in the primary care setting, poses a significant health problem for children and adolescents. The Children's Digestive Health and Nutrition Foundation (CDHNF), in conjunction with the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, have launched a national campaign to educate primary care providers, parents, and children about GERD in children and adolescents.

When diagnosed and treated, GERD in children responds well to the same medications used in adults, particularly proton pump inhibitors (PPIs), said Harland S. Winter, MD, Director of the Pediatric Inflammatory Bowel Disease Center at Massachusetts General Hospital for Children and Harvard Medical School.

There are about 50 million children in the United States under the age of 12. According to marketing surveys, about six million of these children have intermittent symptoms suggestive of GERD. Available data suggest that less than 20% of the children are identified and diagnosed by primary care providers.

On the basis of epidemiologic studies by Dr. Suzanne Nelson, the prevalence of GERD seems to increase with age, from less than 2% of infants to about 7% of adolescents." (*Arch Pediatr Adolesc Med.* 2000;154:150-154). (see **Figure** on page 2.)

> "GERD in children responds well to the same medication used in adults..."

GERD: From child to adult?

Recent studies by Dr. Benjamin Gold and his colleagues have shown that 14% of adult GERD patients recall having taken medications for GERD during childhood, and 20% to 30% report a history of GERD-associated symptoms and conditions during childhood (*J Pediatr Gastroenterol Nutr.* 2002;35: 334-338).

"Because of the inherent problems of retrospective studies requiring recall, this is probably underestimating the number of adult patients with GERD whose symptoms began in childhood," Dr. Winter commented.

Several diagnostic tests have proven useful for evaluating pediatric patients suspected of having GERD. X-rays of the upper gastrointestinal tract provide anatomic information and can help identify anatomic abnormalities that might contribute to reflux, said Dr. Winter. Evaluation with a pH probe can indicate the severity and frequency of reflux and help determine whether reflux occurs during the day, at night, or in association with symptoms such as cough, night terrors, or wheezing.

Endoscopy and biopsy also play a role in evaluating the severity of GERD in pediatric patients, he continued. The approach to biopsy differs between children and adults. Pediatric gastroenterologists obtain biopsies of the stomach, duodenum, and esophagus, for evidence of allergy, eosinophilic esophagitis, or eosinophilic gastritis.

Esophageal motility testing has less of a role in children. Scintiscan studies of the stomach will identify delayed gastric emptying in patients with gastric or motility disorders, said Dr. Winter.

Several years ago, studies demonstrated that acid suppression by H_2-receptor antagonists led to healing of erosive esophagitis in pediatric patients. Separate evaluations of nizatidine and cimetidine showed statistically significant superiority of active treatment over placebo, albeit in small numbers of patients (*J Pediatr Gastroenterol Nutr.* 1997;25:51-55; *J Pediatr Gastroenterol Nutr.* 1989;8:150-156).

Proven results with PPIs

"Like in adults, however, H_2 blockers are not as effective as proton pump inhibitors in suppressing acid production in pediatric patients," said Dr. Winter. "PPIs neutralize intragastric pH to a similar degree in adults and children.

Harland S. Winter, MD

A recent clinical evaluation of lansoprazole in children 1 to 11 years of age with erosive and nonerosive esophagitis showed the PPI reduced the number of days with GERD symptoms at a dosage of 15 mg/day for children weighing less than 30 kg and 30 mg/day for patients weighing 30 kg or more (Tolia, *J Pediatr Gastroenterol Nutr.* 2002; in press).

PPIs also heal erosive esophagitis in pediatric patients whose condition proves to be refractory to H_2-receptor antagonists. The observation has emerged from studies of omeprazole and lansoprazole, and the healing rates in pediatric patients compare favorably to

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Proton Pump Inhibitors Remain Standard for GERD

The emergence of surgical and endoscopic treatment options for gastroesophageal reflux disease (GERD) has yet to impact the role of long-term medical therapy with proton pump inhibitors (PPIs), according to Canadian gastroenterologist Richard H. Hunt, FRCP, FRCP(C), FACG.

Surgery for GERD is associated with significant morbidity and a measurable mortality, and results are operator- and institution-dependent. New endoscopic antireflux procedures have no supporting data from controlled studies and also have a measurable morbidity. In contrast, 16 years of clinical experience and data from multiple large randomized clinical trials support the safety and efficacy of long-term maintenance therapy with PPIs.

"Long-term PPI therapy is not operator dependent; any of us can write the prescription effectively, but it would be wise to advise the patients exactly when to take the drugs," said Hunt, Professor of Medicine at McMaster University Medical Centre in Hamilton, Ont. "We are able to adjust the PPI dose, as well, and we have no real learning curve."

Reviewing the current therapeutic options for GERD, Prof. Hunt noted that comparative studies have shown a "dramatic recurrence of symptoms and esophagitis with the H_2-receptor antagonists, even at high doses, as compared . . . to the proton pump inhibitors." A metaanalysis of 43 clinical trials showed a consistent advantage of PPIs over H_2-receptor antagonists for symptom relief in patients with erosive esophagitis.

> "16 years of clinical experience... support the safety and efficacy of long-term maintenance therapy with PPIs."

A recent review of 12-month remission rates with maintenance therapy for patients with erosive esophagitis showed consistency within the PPI class for maintaining high remission rates in the range of 85% to 91% (*Drugs*. 2002;62: 1173-1184). In contrast, long-term healing with H_2-receptor antagonists was similar to that achieved with placebo, Prof. Hunt noted.

Moreover, PPIs have demonstrated remarkable consistency in the dose required to maintain healing, including one study of patients followed for more than 10 years (*Gastroenterology*. 2000;118: 661-669).

"The effect of the PPIs is considerably stable, with no obvious evidence of loss of effect over time," said Prof. Hunt. "Only a small proportion of patients needed to have an increase in dose over time."

When patients fail to achieve an adequate response with the starting dose of a PPI, a physician should evaluate patient compliance before contemplating any change in therapy, he continued.

Adherence and success

"In my clinical experience, the majority of patients who are not doing well on a PPI have not been taking it correctly, either because they have chosen not to or because they were not properly instructed by their primary care physician in the first place," said Prof. Hunt. "We have to ask at what time they take their treatment. Because of the short plasma half-life of proton pump inhibitors, it is important that the drugs are taken in the hour before the first meal of the day, on an empty stomach."

If a patient is taking the PPI correctly and still has breakthrough GERD symptoms, taking a second dose of the PPI in the hour before the evening meal is the appropriate next step, he continued. If symptoms remain poorly controlled with BID dosing, intraesophageal pH monitoring during PPI therapy is warranted to determine whether pathologic acid reflux is occurring. If the pH monitoring documents reflux, a review of the dose and timing is needed, and rarely is a dose increase required. A switch to another therapy should be considered if the patient does not have acid reflux.

"We now have more than 16

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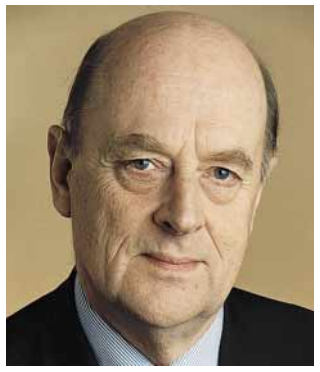

Professor Richard H. Hunt

GERD Often Overlooked

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findings from a metaanalysis of healing in adults (*J Pediatr*. 1993;123:148-154; *Dig Liver Dis*. 2000;32:660-666; Tolia. *J Pediatr Gastroenterol Nutr*. 2002; in press).

A study in adults with GERD and asthma, reported at the 2002 American College of Gastroenterology meeting, supported a potential new indication for use of PPIs in management of patients with chronic and recurrent asthma. The study involved adult patients with asthma randomized to treatment with lansoprazole or placebo. The PPI therapy led to a significant decrease in asthma exacerbations.

"This study suggests that in some patients with asthma, acid may in fact be a trigger for the initiation of an attack," said Dr. Winter. "It remains to be established in additional trials whether or not treatment with a PPI will decrease the number of hospitalizations and improve quality of life."

Flavored formulation for children

Since most of the medications used to treat children are never formally tested in the pediatric population, resources have not been allocated to find palatable formulations that children will accept. Until recently, choosing among the available PPIs had been a problem in the management of pediatric patients with GERD. Many younger children have difficulty swallowing capsules and tablets, and liquid formulations containing bicarbonate have an unpleasant taste that many patients refuse to take, said Dr. Winter.

Development of a strawberry-flavored formulation of lansoprazole should help obviate many pediatric patients' objections to PPI therapy, he added. Both the 15- and 30-mg doses are available in the flavored formulation.

In summarizing the current knowledge about GERD in pediatric patients, Dr. Winter noted that 98% of infants less than 12 months of age with regurgitation are completely better by 15 months of age and do not require intervention. When symptoms do not resolve by 18 months, patients should be referred to a pediatric gastroenterologist for consultation.

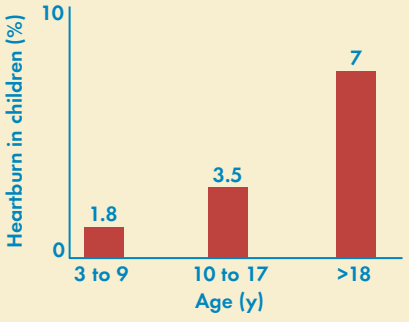
"We suspect that children over the age of two years with persistent or recurrent symptoms may become adults with complications of GERD," Dr. Winter concluded. "Additional studies are needed to confirm this observation, as there are effective medications available for children with GERD in formulations they can tolerate."

Dr. Winter's 25 years of clinical experience have raised two areas of concern: (1) a strong family history of GERD and (2) intermittent symptoms of heartburn or dysphagia that may disappear for months but interfere with activities.

"My concern is that we don't respond to periods of symptoms, and by waiting, the child goes into a period of feeling better," Dr. Winter said of children with symptoms that wax and wane. "The process of injury and repair over many years may cause chronic sequelae, such as inflammation of the esophagus and/or stricturing. The history of symptoms and the family history are two features that are important to understand."

To obtain more information about GERD in children, visit the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition's web site at www.naspgn.org.

Figure. Prevalence of GERD



GERD in adults

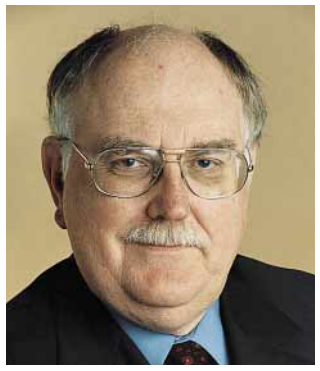
Adult refluxers vs. nonrefluxers with childhood symptoms

• History of fundoplications	4%
• History of GERD medications	14%
• History of dysphagia, heartburn, water brash	21% - 29%
• History of asthma and GERD	22%

GERD = gastroesophageal reflux disease

Sources: Gibbons. *Gastroenterology*. 122; 178-187:2002. Hu FZ, et al. *JAMA*. 2000; 284:325-324. Nelson SP, et al. *Arch Pediatr Adolesc Med*. 2000; 154:673-678. Waring. *J Pediatr Gastro Nutr*. 2002; in press.

Healing and Prevention of NSAID-associated Gastric Ulcers in Elderly Patients



David A. Peura, MD

The availability of specific inhibitors of cyclooxygenase-2 (COX-2) has introduced new considerations and risks that physicians must weigh when choosing a strategy for prevention and management of gastric injury due to nonsteroidal antiinflammatory drugs (NSAIDs).

Within the context of an increasingly complicated clinical situation, proton pump inhibitors (PPIs) figure prominently in strategies to achieve gastrointestinal (GI) protection.

"PPIs accelerate the healing of NSAID-associated gastric and duodenal ulcers," said David A. Peura, MD, FACG, FACP, Professor of Medicine at the University of Virginia Health Sciences Center in Charlottesville. "They can prevent the recurrence of gastric and duodenal ulcers. Most importantly, PPIs maintain that benefit, even in the subgroup of individuals taking concomitant NSAIDs and low-dose aspirin."

GI protection has major implications for the growing population of regular users of GI drugs, particularly the rapidly increasing population of older individuals. Between 10,000 and 16,000 people die each year from NSAID-induced side effects, and an additional 100,000 people are hospitalized because of NSAID-related side effects (National Center for Health Statistics. 1998; *J Rheumatol*. 1999;26:18-24).

"That accounts for 30 to 50 deaths and about 300 hospitalizations every single day due to NSAID gastrointestinal side effects. That constitutes an epidemic," said Dr. Peura. "More people have died and continue to die from NSAIDs than have died since West Nile virus was first described in the United States, but we read about West Nile virus in the headlines. This is a silent epidemic, something we're really not reading about."

Need for risk stratification

Control of the epidemic begins with risk stratification, Dr. Peura noted. With respect to use of NSAIDs, patients with a history of complicated ulcer have a 13.5 times greater chance of developing another complication if they begin NSAID therapy. Other high-risk groups include patients taking multiple NSAIDs, high-dose NSAIDs, and anticoagulants, and those with a history of uncomplicated ulcer. Age greater than 70 years also is associated with an increased risk for NSAID-associated ulcer complications (see **Figure**).

> "...PPIs figure prominently in strategies to achieve gastrointestinal protection."

"Interestingly, there is a cumulative risk over time," said Dr. Peura. "The longer somebody takes an NSAID, the more likely the person is to have a problem. However, the period of greatest risk seems to be within the first 3 months of starting the medication. That's a very important point, because sometimes we get lulled into this false sense of security, thinking that since a patient is only going to be on the NSAID for a short period of time, we can get away with it, even if he has a risk for complications. Also, most patients who develop a complication are asymptomatic, so we can't use symptoms to risk-stratify."

In patients with NSAID-induced gastric injury who continue their NSAID, PPIs heal ulcers in 75% of cases after 8 weeks of therapy, which compares with a healing rate of about 50% with an H_2-receptor antagonist (*Arch Intern Med*. 2000;160:1455-1461).

"The good news is that three-fourths of ulcers heal at 8 weeks; the bad news is that three-fourths of ulcers heal at 8 weeks," said Dr. Peura. "Unlike the situation where NSAIDs are discontinued, we may need to treat with the PPI for at least 12 weeks, if NSAIDs are continued, to ensure that ulcers heal."

PPIs also have demonstrated the ability to prevent ulcer recurrence and ulcer-associated complications in NSAID users. PPIs have proved superior in placebo-controlled trials and in comparison to half-dose misoprostol, which until recently had been the only therapy approved by the Food and Drug Administration (FDA) for prevention of ulcer recurrence (*Gastroenterology*. 1996;110:A86, *Arch Intern Med*. 2002;162:169-175).

In comparison to placebo and full-dose misoprostol, the PPI lansoprazole maintained its beneficial effect in the subgroup of patients taking low-dose aspirin with their NSAIDs, Dr. Peura noted. Misoprostol also demonstrated efficacy but was associated with a higher incidence of adverse events, compared to lansoprazole.

Aspirin and GI risk

The impact of aspirin on GI risk came into focus in a recent study that evaluated ulcer-bleeding recurrence. Patients with bleeding ulcers were treated with a PPI to heal the ulcer, and *H. pylori*, when present, was eradicated. The patients were then randomized to low-dose aspirin plus lansoprazole or to low-dose aspirin plus placebo. Patients randomized to aspirin alone had a 15% incidence of GI bleeding in the subsequent 12 months, compared with 1.6% of patients who received aspirin plus the PPI (*N Engl J Med*. 2002; 346:2033-2038).

"Clearly, you can see the impact of aspirin in this high-risk group of patients," said Dr. Peura. "I think the concept of low-dose aspirin causing gastrointestinal problems is something that is not well appreciated in the primary care setting."

Coxibs, or selective COX-2 inhibitors, are a new class of presumably safer NSAIDs. They spare COX-1, the enzyme responsible for prostaglandin synthesis in the GI mucosa, platelets, and kidneys. COX-2 initially was thought to be an enzyme that was induced in response to inflammation. Subsequently, COX-2 was found to be constitutive to the brain, the kidney, pancreas, female reproductive system, and vascular endothelium.

Switching a patient from a traditional NSAID to a "mucosal friendly" COX-2 inhibitor is another strategy that can be used to prevent recurrence of ulcers and complications. Two studies have suggested that a coxib or a combination of an NSAID and a PPI are equally effective in preventing subsequent complications. However, patients in these studies did not use aspirin, which is known to reduce the protective effects of coxibs (*Gastroenterology*. 2001;102:A104; *Gastroenterology*. 2001;120: A143).

In addition, the coxibs will not heal ulcers and in fact may delay ulcer healing in a fashion similar to traditional NSAIDs, said Dr. Peura. Therefore, a PPI is still needed to promote ulcer healing.

The effects of COX-2 in vascular endothelium have emerged as a particularly intriguing aspect of strategies to improve GI protection in NSAID users.

"A nonselective NSAID blocks platelets, which is a prothrombotic effect, and also blocks the endothelial pathway, which is antithrombotic, resulting in a balanced system," said Dr. Peura. "If you use a selective agent, you spare the prothrombotic effect of platelets, while at the same time you block the antithrombotic effect in the endothelium. In theory this might lead to an unbalanced situation that promotes thrombogenesis."

COX-2 inhibitors' impact unclear

Results of two large, randomized clinical trials of selective

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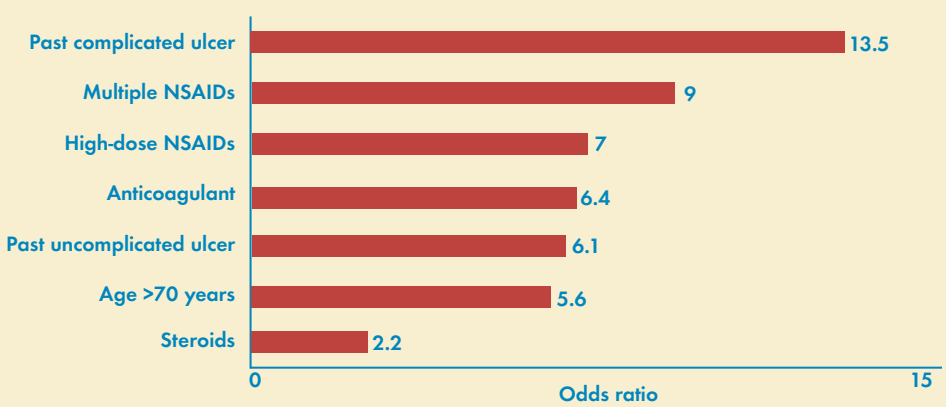
Figure. What Are the Risk Factors for NSAID-Associated Ulcer Complications?



- Risk greatest within first 3 months of use
- Majority of patients who develop a serious GI adverse event on NSAIDs are *asymptomatic* prior to event

NSAID = nonsteroidal antiinflammatory drug; GI = gastrointestinal

Sources: Gabriel SE, et al. *Ann Intern Med*. 1991;115:787-796. Garcia Rodriquez LA, Jick H. *Lancet*. 1994;343:769-772. Silverstein FE, et al. *Ann Intern Med*. 1995;123:241-249.

Healing and Prevention

Continued from previous page

COX-2 inhibitors have added to the uncertainty surrounding GI protection. A trial comparing rofecoxib and naproxen showed a 50% reduction in upper GI events, GI bleeding, and complicated upper GI events, in favor of rofecoxib (*N Engl J Med*. 2000;343:1520-1528). However, a study comparing celecoxib and conventional NSAIDs produced mixed results, said Dr. Peura. At 6 months, patients randomized to the COX-2 inhibitor had a trend toward a lower incidence of ulcer-related complications (*JAMA*. 2000;284:1247-1255), but 12-month data submitted to the FDA showed no difference between treatment groups.

The contributions of low-dose aspirin could explain the disparate results between the studies of the COX-2 inhibitors, said Dr. Peura. In the rofecoxib study, concomitant aspirin was not allowed. In the celecoxib study, about 20% of the patients also took aspirin. In the subset of patients taking aspirin, the incidence of ulcer complications did not differ between the celecoxib and NSAID groups.

Aspirin also might have figured into the differing cardiovascular results observed in the rofecoxib and celecoxib trials. In the rofecoxib study, wherein aspirin use was prohibited, patients treated with the COX-2 inhibitor had more heart attacks than did patients treated with the conventional NSAID, which shares aspirin's antiplatelet activity. In contrast, the heart attack rate was similar between treatment groups in the celecoxib trial.

Results of the two trials of COX-2–inhibitor therapy emphasize that "patients at high risk for cardiovascular disease are going to require aspirin prophylaxis," said Dr. Peura. "COX-2 inhibitors and conventional NSAIDs are not substitutes for aspirin."

A risk-adjusted approach to prevention and management of GI events offers one potential strategy for dealing with the sometimes disparate data from clinical studies. Under one such schema, developed by Dr. Mark Fendrick (*Pharm Ther*. 2002; 27:579-582), a patient at low risk for cardiovascular disease and GI events might be managed with a generic NSAID, said Dr. Peura.

A person who has average or high risk for a GI event but is not taking aspirin might get a COX-2 inhibitor or perhaps an NSAID if already on a PPI for some other reason. A patient who requires aspirin for cardiovascular risk but has a low risk for a GI event might be managed with an NSAID and a PPI; whereas one with a higher risk for GI events and who also needs aspirin for cardiovascular protection will require a PPI regardless of whether a COX-2 inhibitor or an NSAID is used, said Dr. Peura.

Proton Pump Inhibitors

Continued from page 2

years of experience and more than 219 million patient treatments in 98 countries worldwide," he stated. "There are no obvious signals for adverse events, and particularly none related to instability of the gastric mucosa or of gastric adenomas, adenocarcinoma, or carcinoids."

Surgical option

Despite the excellent track record of medical therapy for GERD, considerable interest has surrounded the development of nonmedical alternatives. Interest in surgical options has centered on laparoscopic fundoplication. The procedure has an overall success rate of about 85%, according to a published review cited by Prof. Hunt (*Am J Gastroenterol*. 1999;94:1721-1723).

An advantage of laparoscopic fundoplication is its ability to control acid and bile reflux, as well as regurgitation. However, Prof. Hunt pointed out that the procedure has a complication rate of about 9% and a 0.2% mortality rate. Between 5% and 6% of patients have dysphagia following surgery, and the reoperation rate is almost 1%.

A published survey of patient satisfaction with laparoscopic surgery for GERD in community practice provided additional insights into the efficacy and safety of surgical intervention (*Gastroenterology*. 2001; 120[suppl 1]:A16). Two years after surgery, 58% of patients said they were satisfied with the results, and 29% said they were "somewhat satisfied." The remaining 13% were dissatisfied.

Other findings from the survey included new-onset dysphagia, bloating, and gas in 67% of patients and, importantly, a need for ongoing medical therapy in 27%. Prof. Hunt said 8% of patients required dilatation procedures because the fundoplication was too tight, and 7% had repeat surgery.

Several other studies have shown that a high proportion of patients continue to require medication for GERD symptoms after surgery. One of the largest studies involved 2,382 Veterans Affairs patients who were followed for a minimum of 6 months after surgery. Medical records showed that 34% of the patients were taking a PPI and 23% were being treated with an H_2-receptor antagonist.

Endoscopic strategies untested

In reviewing endoscopic approaches to the treatment of GERD, Prof. Hunt pointed out that data on the efficacy of the procedures are limited to uncontrolled, unblinded, pilot studies.

The Stretta procedure has resulted in improved GERD symptom scores for up to 12 months without medication (*Gastrointest Endosc*. 2002;55:149-156). However, a substantial amount of sedation is required for a procedure that lasts about an hour. Ten of 118 patients had acute but self-limiting complications. Prior to surgery, 31% of patients had esophagitis, and, 6 months after surgery, 25% of patients still had esophagitis. Almost a third of patients had resumed PPI therapy a year after the endoscopic procedures.

In a multicenter clinical trial, the transoral procedure of endoscopic gastroplasty led to significant reductions in the incidence of heartburn and regurgitation during the first 6 months of follow-up, but the proportion of time with pH below 4.0 did not change significantly from baseline (*Gastrointest Endosc*. 2001;53:416-422). A two-year follow-up in another study also showed a reduction in heartburn and regurgitation scores. However, only 25% of patients had completely discontinued PPI therapy, and 28% required half-dose therapy on a regular basis.

The newest endoscopic procedure is the injection of an implantable biopolymer that employs a low-viscosity solution. This precipitates as a spongy mass that is neither biodegradable nor immunogenic and does not shrink after injection or migrate through the bloodstream or lymphatic system (*Gastrointest Endosc*. 2002; 55:335-341). The efficacy of the procedure is not yet clear, said Prof. Hunt, and clinical results have not been widely reported.

Endoscopic procedures are associated with a measurable degree of morbidity. The Stretta technique has been associated with fever, chest pain, dysphagia, pleural effusion, mucosal tear, perforation, and aspiration, said Prof. Hunt. Complications associated with endoscopic gastroplasty include pharyngitis, abdominal pain, chest pain, mucosal tear, hypoxia, bleeding, and suture perforation. Limited experience with the implantable biopolymer procedure has led to chest pain and dysphagia in some patients.

"[Endoscopic procedures for GERD] are technically challenging, especially the gastroplasty procedure," Prof. Hunt concluded. "There is often a need for prolonged sedation and anesthesia, and the general clinical application is premature."

"The risk-benefit ratio is still heavily in favor of medical therapy," he added in response to a question that followed his presentation. "Clearly, if we're referring our patients for surgery, we want to know the operator and we want to know the institution in which the surgery is going to be undertaken. There are good data that tell us those factors have a significant impact on the ultimate outcome of surgery."

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