Heartburn Requiring Frequent Antacid Use May Indicate Significant Illness

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Background: Many otherwise healthy individuals with episodic heartburn self-medicate with over-the-counter antacids. We evaluated clinical characteristics of subjects who had never been medically diagnosed as having any upper gastrointestinal tract disorder and who used antacids for symptomatic relief of heartburn.

Subjects and Methods: Subjects with at least 3 months of frequent heartburn relieved by antacids, and with heartburn on at least 4 of 7 days during the week prior to study entry, had their medical history and gastrointestinal pathological characteristics recorded. Tests included esophagogastroduodenoscopy, esophageal motility and sensitivity studies, and 24-hour pH monitoring.

Results: Of 178 subjects screened, 13 were excluded on the basis of other gastrointestinal diseases at baseline, including diffuse esophageal spasm, peptic ulcer disease, dysplastic columnar metaplasia of the esophagus (Barrett’s esophagus), and adenocarcinoma. Ten subjects were ineligible because of insufficient baseline heartburn. The remaining 155 eligible subjects had heartburn for an average of 11 years. Forty-seven percent had daily symptoms and 70% described heartburn severity as moderate, even though on endoscopy most (53%) had normal-appearing esophageal mucosa (grade 0 or 1). Esophageal acid sensitivity was present in 86% of subjects. Mean lower esophageal sphincter pressures and esophageal contractile amplitudes were at the lower limits of normal and total esophageal acid contact time was slightly increased.

Conclusions: Chronic heartburn can reflect a wide range of diagnostic findings, including important underlying pathological features, and may warrant a full medical examination to detect such abnormal conditions and to permit selection of appropriate therapy.

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ANTACIDS ARE widely used for heartburn, even though they are ineffective for many conditions associated with heartburn-like symptoms, including peptic ulcer disease and serious esophageal disease (e.g., erosive gastroesophageal reflux disease [GERD]), strictures, and columnar metaplasia of the esophagus (hereafter, Barrett’s esophagus).1 Because heartburn may be dismissed as trivial, many affected individuals do not consult physicians and may have experienced symptoms for years.2,3 No adequate data fully characterize upper gastrointestinal tract abnormalities in regular antacid users.

Our objective was to comprehensively examine the upper digestive structure and function in otherwise healthy antacid-using individuals who had not previously sought medical attention for long-term heartburn. Some of the study results were presented at the meeting of the American Gastroenterological Association, May 20, 1996.4

This article is also available on our Web site: www.ama-assn.org/internal.
SUBJECTS, MATERIALS, AND METHODS

STUDY DESIGN

Adults with at least a 3-month history of frequent antacid-treated heartburn with no previous professional medical diagnostic or therapeutic intervention for their upper digestive tract symptoms were eligible for this study. Subjects were recruited at the point of antacid purchase or via advertising. Subjects were excluded for any other major illness or for gastric or duodenal ulcers larger than 5 mm. The subjects' regular use of any medication affecting gastrointestinal tract function was excluded. The study was conducted at 2 sites in the United States and was approved by institutional review boards for each. All patients provided written informed consent.

Baseline medical history taking, physical examinations, and laboratory screening were done. Heartburn and reflux-related symptoms (heartburn, dysphagia, odynophagia, cough, sore throat, noncardiac chest pain, regurgitation, wheezing, hoarseness, water brash, nausea, decreased appetite, indigestion, belching, halitosis, and other symptoms) were recorded at baseline.

One week of self-directed use of calcium carbonate provided prestudy baseline data. Daytime and nighttime heartburn frequencies were assessed. Calcium-carbonate antacids used in the study were formulated as swallowable tablets. No other antacids were allowed. Lifestyle modifications at baseline continued unmodified throughout the study. Heartburn frequency and antacid consumption during the trial were monitored using daily diary cards. Heartburn severity was assessed using a visual analog scale from 0 mm (no heartburn) to 100 mm (unbearable heartburn). Eligible subjects with heartburn for at least 4 of 7 consecutive days began diagnostic tests. Sample size was determined by the number of subjects projected for enrollment during a 6-month period.

DIAGNOSTIC TESTS

During the diagnostic phase, subjects underwent the following tests.

Esophagogastroduodenoscopy

Examination included determination of the presence and size of hiatal hernia, ulcerations, and the adapted Hetzel grading of esophagitis. Barrett’s esophagus was sought and confirmed via a biopsy specimen of the suspected metaplastic areas.

Lower Esophageal Sphincter and Esophageal Motility Measurements

Lower esophageal sphincter (LES) characteristics and esophageal motility measurements were obtained (Synectics system, Medtronic Synectics, Shoreview, Minn). Data included mean LESP (millimeters of mercury), mean velocity (centimeters per second), mean LESP relaxation ([LESP – residual pressure]/LESP × 100 = % LESP relaxation), mean wave amplitude (millimeters of mercury), and mean wave duration (seconds).

Bernstein Acid Perfusion Test

The perfusing catheter was positioned 3 cm above the LESP. Saline (120 drops per minute) was infused into the esophagus for 10 minutes, followed by up to 20 minutes of 0.1N hydrochloric acid (120 drops per minute) until a sensation of heartburn, warmth, pain, or discomfort was reported. Saline was reinfused for up to 10 minutes to assess disappearance of discomfort. Data reported were timed responses to the saline and acid infusions and relief of discomfort by the second saline infusion.

Balloon Distention

Esophageal sensitivity to balloon distention was assessed with a latex balloon 5 cm above the LESP. The balloon was distended with air at 1 mL increments every 3 seconds to a total volume of 15 mL. Sensory threshold was recorded when subjects first perceived sensation, and pain threshold (defined as uncomfortable or painful) was also documented. Sensory and pain thresholds were recorded.

pH Monitoring

Twenty-four-hour pH monitoring included number of reflux episodes (total, upright, supine, postprandial, and episodes lasting >5 minutes), duration of the longest reflux episode, and percentage of time that the pH was below 4 (total, upright, supine, and postprandial). Use of antacids was not permitted during the 24-hour pH monitoring study.

daily heartburn during the previous year. Fifty-six percent described heartburn that worsened with the use of caffeine.

Most subjects reported at least 1 secondary symptom of reflux disease that included regurgitation, chest pain, or water brash. Many also reported 1 or more alarm symptoms, including dysphagia, hoarseness, odynophagia, or wheezing (Figure 3).

RESULTS OF DIAGNOSTIC TESTS

Esophagogastroduodenoscopy

Endoscopy revealed hiatal hernia in 57% of subjects and nondysplastic Barrett’s esophagus in 6% (data not shown). Fifty-three percent had essentially normal esophageal muscularis (grade 0 or grade 1); the remainder had erosive esophagitis (although two thirds had only mild erosive changes).

LESP and Esophageal Motility Measurements

The average LESP was low normal (mean, 11.8 mm Hg; median, 10.3 mm Hg); almost half (49%) of the subjects had subnormal mean LESPs (<10 mm Hg). Mean esophageal wave amplitude was subnormal at 60 mm Hg; 32% of subjects had low-amplitude esophageal contractions (<42 mm Hg).

Esophageal Sensitivity Tests

Results of tests of increased esophageal sensitivity, the Bernstein acid perfusion test, and esophageal balloon dis-
tention test were positive in 86% and 41% of subjects, respectively. There were no important differences in balloon distention thresholds between subjects with normal esophageal mucosa compared with those with grade 3 to 4 esophagitis.

**COMMENT**

This study demonstrates that individuals with long-term heartburn who use antacids have a broad spectrum of anatomical, physiological, and endoscopic diagnoses, that range from essentially normal findings to severe pathological conditions, including peptic ulcer disease, various grades of erosive esophagitis, Barrett’s esophagus, and cancer. None of the subjects in this study recognized the potential adverse significance of alarm symptoms, such as odynophagia, dysphagia, hoarseness, and wheezing. Few had reported these symptoms to physicians in the past, and none had received diagnostic or therapeutic intervention. There is an apparent need for education of the public regarding the potential significance of long-term heartburn and related symptoms.

Heartburn for an average of 11 years confirmed chronicity, even in this ostensibly preclinical reflux disease. Hiatal hernia in more than half of the subjects confirms the widely accepted relationship between hiatal hernia and GERD.

**pH Monitoring**

Twenty-four–hour pH monitoring (Figure 4) indicated moderate but quite variable acid exposure, ie, esophageal pH of 4 or higher (median, 6.7%; range, 0.1%-68.4%). Almost a third of the subjects had more than twice the normal acid exposure (>6%) as defined by our laboratory.

Erosive esophagitis was observed in approximately half of the subjects. Most had enhanced esophageal acid sensitivity demonstrated on Bernstein testing. Our findings support the results of a small earlier study of frequent antacid users in a Department of Veterans Affairs setting that demonstrated erosive esophagitis in more than half of those with heartburn and positive acid perfusion test results in 90%. Our results also support findings from a large European multicenter study in primary care settings of clinical features and endoscopic diagnoses in 806 subjects with refluxlike symptoms. Similar to 93% of our subjects, 90% of the Europeans rated their heartburn as moderate to severe. Whereas 67% of the Europeans had daily symptoms, mainly retrosternal burning and epigastric pain, 47% of our subjects reported daily heartburn. Endoscopic examination in the European study showed that 41% of subjects had mild to moderate esophagitis, but only 4% had severe esophagitis with ulceration. Fifty-three percent of subjects in our study had normal esophageal mucosa, 31% had mild esophagitis, and 16% had more severe (grade 3 or 4) erosive esophagitis. Finally, the results of our study agree with another US study of 234 people with heartburn, only 9% with any erosions, ulcerations, or strictures. Thus, most long-term heartburn does not indicate serious disease, but almost 50% of subjects do have some degree of erosive mucosal injury that possibly might benefit from treatment with prescription-strength medication.
It concerns us that 6% of subjects in the present study had nondysplastic Barrett’s esophagus and 2 subjects were excluded at screening because of dysplastic Barrett’s esophagus or Barrett’s esophagus with cancer. Barrett’s esophagus may complicate long-term reflux disease via replacement of normal esophageal squamous epithelium with specialized columnar mucosa. Because of the recognized association between Barrett’s esophagus and the development of esophageal adenocarcinoma, the identification of patients with Barrett’s esophagus is of clinical concern. Barrett’s esophagus may be associated with fewer symptoms than other forms of GERD. Lower esophageal sphincter measurements were at the lower end of the normal range in the present study, although even a 2 to 3 mm Hg LESP may provide some barrier to reflux. The findings of increased acid contact time in our subjects with frequent heartburn reflect increased gastroesophageal reflux and are similar to those of Joelson and Johnsson, who found frequent heartburn associated with elevated esophageal mucosal acid exposure. Although most users of over-the-counter (OTC) antacids have gastroesophageal reflux–related symptoms, most do not consult physicians. Little correlation exists between disease or symptom type or severity and endoscopic appearance of the esophagus. Antacids may be useful for the short-term relief of heartburn. However, they are probably not effective in healing esophagitis or preventing possible complications of reflux disease. Antacids are generally safe, but continuous high doses can cause acid rebound, milk-alkali syndrome, metabolic alkalosis, and exacerbation of hypertension or congestive heart failure if sodium content is high. Antacids can also adversely affect lower gastrointestinal tract function; magnesium-containing antacids may cause diarrhea, while aluminum-containing antacids may cause constipation. Antacids may produce drug-drug interactions by elevating gastric pH and thereby decreasing drug absorption (eg, digoxin), binding to drugs (eg, tetracycline), and increasing urinary pH and inhibiting drug elimination (eg, quinidine). Nevertheless, the size of the antacid market and wide acceptance of antacids as efficacious confirms their utility for symptomatic treatment of heartburnlike dyspepsia. Long-term requirements for symptom control by OTC medications for symptomatic relief may signify underlying pathological conditions, and such medications may mask serious disease. Individuals with persistent heartburn who have warning symptoms of complicated reflux disease, such as regurgitation, dysphagia, odynophagia, or wheezing, or persistent symptoms after 4 to 6 weeks of lifestyle modifications and use of OTC medications (now including the OTC histamine₂-receptor antagonists) may have significant erosive esophagitis or other complications of reflux disease. Since early diagnosis and treatment of complicated reflux disease may prevent clinical deterioration, regular users of antacids should be educated regarding the possible significance of their symptoms. Improved public awareness possibly could avert complications of reflux disease. Since early diagnosis and treatment of complicated reflux disease may prevent clinical deterioration, regular users of antacids should be educated regarding the possible significance of their symptoms. Improved public awareness possibly could avert complications of reflux disease.

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