Introduction

Heartburn, a substernal burning rising up from the stomach to the lower chest and neck (1), is the primary symptom of gastroesophageal reflux disease (GERD). Heartburn is one of the most common complaints of patients presenting to physicians, with approximately 40% of the US population experiencing heartburn at least once per month and about 10% having it daily (2–4). Frequent heartburn is an early-warning symptom in the pathological continuum of GERD and is a risk factor for esophageal adenocarcinoma (Figure 1). Endoscopic evaluation in some studies, however, has indicated that only about one half of patients with frequent heartburn have erosive esophagitis, and less than 15% of patients with nonerosive esophagitis experience worsening of their symptoms over 6 months (4). Patients with heartburn, but without alarm symptoms, may be candidates for self-
treatment with over-the-counter medications. Atypical symptoms that might prompt referral to a specialist are listed in Table 1.

For many patients, heartburn associated with GERD is a chronic symptom that significantly impairs quality of life (5,6). The major focus of medical therapy is to reduce acid production, thereby decreasing symptoms of chronic heartburn and leading to significant improvement in patient quality of life (7). Proton pump inhibitors (PPIs) have been a major advance and are helping physicians and their patients move toward this goal. Optimal therapy requires an understanding of the mechanism of acid production/secretion, the pathophysiology of heartburn, the differences in the mechanisms of action and efficacy of the most widely used heartburn medications, and short- and long-term safety issues regarding heartburn therapy. Additionally, physicians should be able to counsel patients and reinforce the safety and benefits of PPI use.

**PATHOPHYSIOLOGY AND CAUSES OF HEARTBURN**

Heartburn results when reduced lower esophageal sphincter (LES) pressure allows abnormal reflux of gastric material into the esophagus, causing pain and irritation (8). Several pathophysiologic mechanisms that predispose patients to heartburn are listed in Table 2. Since heartburn is most often a symptom of GERD, it is important that heartburn not be ignored: Untreated or insufficiently controlled GERD can result in long-term problems such as erosive esophagitis, Barrett’s esophagus, and esophageal ulcer (9,10).

Many factors are known to aggravate or precipitate heartburn. Some common offenders are caffeine, chocolate, citrus and tomato products, fat, peppermint, and spicy foods (4,11). Lifestyle factors include bending, lifting, pregnancy, exertion, smoking, wearing tight clothing, and eating meals close to bedtime (4,12,13). Obesity has also been associated with heartburn; however, weight reduction has not been clearly shown to resolve symptoms (13). Finally, certain medications can decrease LES pressure and potentially increase reflux symptoms (Table 3) (13).

![Image of a diagram showing the Pathophysiologic Continuum for heartburn: Acid Reflux (Heartburn) → Erosive esophagitis → Barrett’s esophagus → Adenocarcinoma.](imageURI)

**Table 1**

<table>
<thead>
<tr>
<th>Gastroesophageal Alarm Symptoms (4,36).</th>
</tr>
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<tbody>
<tr>
<td>• Dysphagia</td>
</tr>
<tr>
<td>• Early satiety</td>
</tr>
<tr>
<td>• Frequent nausea</td>
</tr>
<tr>
<td>• Frequent vomiting</td>
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<tr>
<td>• Gastrointestinal bleeding</td>
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<tr>
<td>• Weight loss</td>
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**Table 2**

<table>
<thead>
<tr>
<th>Pathophysiologic Mechanisms That Predispose to Heartburn</th>
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<tbody>
<tr>
<td>• Abnormal antireflux barrier</td>
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<tr>
<td>• Impaired esophageal barrier</td>
</tr>
<tr>
<td>• Increased intra-abdominal pressure</td>
</tr>
<tr>
<td>• Increased intragastric volume or acid load</td>
</tr>
<tr>
<td>• Gastric distention</td>
</tr>
<tr>
<td>• Duodenal-gastric reflux</td>
</tr>
<tr>
<td>• Gastric hypersecretion</td>
</tr>
<tr>
<td>• Injury to esophageal tissue barrier</td>
</tr>
<tr>
<td>• Hiatal hernia</td>
</tr>
</tbody>
</table>
Table 3
Medications That May Aggravate Heartburn

- Alpha-adrenergic blockers
- Anticholinergics
- Beta-adrenergic agonists
- Calcium channel blockers
- Diazepam, alprazolam
- Narcotics
- Progesterone
- Theophylline


Although absence of the above factors may reduce the occurrence of heartburn, many patients find it difficult or impossible to avoid these triggers consistently.

MECHANISM OF ACID PRODUCTION AND SECRETION

The parietal cell, located in the gastric gland of the stomach, produces and secretes gastric acid (14). The resting parietal cell is characterized by the presence of large amounts of smooth surface membranes called tubulovesicles, as well as a small infolding of the apical membrane known as the secretory canaliculus, which is continuous with the lumen of the stomach (14). Within the tubulovesicular membrane, hydrogen ion/potassium ion-adenosine triphosphatase (H⁺/K⁺ ATPase), or proton pump, when activated, transports hydrogen (H⁺) out of the parietal cell (14).

Stimulation of the parietal cell initiates the fusion of tubulovesicles with the secretory canaliculus, increasing its surface area and volume (14). Concurrently, the proton pump translocates from the cytoplasmic tubulovesicular membrane to the canalicular membrane (14). H⁺, adenosine triphosphate (ATP), and magnesium (Mg⁺) subsequently bind to the proton pump (14). Transfer of the terminal phosphate of ATP to the proton pump produces a conformational change in the enzyme that reduces the affinity for H⁺ and increases the relative affinity for K⁺ (14). Consequently, an H⁺/K⁺ exchange occurs as H⁺ is released into the lumen and K⁺ in the gastric juice becomes bound to the proton pump (14). Dephosphorylation of the proton pump returns the enzyme to its original conformation state, which leads to the release of K⁺ into the cytoplasm (Figure 2) (14).

Certain mediators stimulate acid secretion by interacting with one another and by binding to their respective receptors in the parietal cell to form intracellular messengers. The release of acetylcholine, the activation of histamine-2 (H₂) receptors, and the secretion of gastrin all stimulate H⁺ ion generation and production of gastric acid (15).

TREATMENT OF HEARTBURN

Antacids, H₂ receptor antagonists (H₂RAs), and PPIs are among the pharmacologic options for treating heartburn. Each of these therapeutic classes has a distinct mechanism of action. Most antacids are available without a prescription. Despite the many brands on the market, antacids are all based on 4 active ingredients in various strengths and combinations: magnesium

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The PPIs include omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole. The mechanism of action of these weak base prodrugs involves 3 stages: (1) PPIs selectively accumulate in the acidic secretory canaliculus of the active parietal cell (Figure 3) (2). At that site or on the surface of the ATPase in the cell membrane, they undergo H⁺-catalyzed conversion to an active form (3). Upon activation, PPIs covalently bind to an external cysteine in the transport region of the proton pump. This inhibits acid secretion, no matter what the stimulus (Figure 4) (15). PPIs accumulate, are activated, and work where needed, directly inhibiting the acid-producing proton pump regardless of whether acid secretion was stimulated by food, medication, or other factors. This unique trait of selective accumulation and action has prompted some clinicians, including Dr. George Sachs, one of the authors of this article, to apply the term “smart drugs” to PPIs.

PPIs provide symptomatic relief to up to 90% of patients with frequent heartburn; this is superior to the efficacy of antacids or H₂RAs (15). PPIs are usually taken once daily, less frequently than other heartburn therapies (21). Many patients achieve symptomatic relief after the first dose, but optimal response to PPIs occurs after 2 to 3 days of treatment (15). Patients frequently remain symptom free with PPI therapy for up to 24 hours (15).

SAFETY OF ACID-REDUCING THERAPIES

Adverse Effects

Since heartburn can be a chronic problem necessitating long-term therapy, safety is a major concern in the choice of treatment. There are several potential side effects associated with the use of antacids: 1) Sodium bicarbonate can alter systemic pH. 2) Calcium carbonate can stimulate acid production through release of gastrin and can also cause hypercalcemia. 3) Aluminum hydroxide and magnesium hydroxide can alter

hydroxide, calcium carbonate, aluminum hydroxide, and sodium bicarbonate (11). Antacids neutralize gastric acid, which increases intragastric pH, leading to substantial inhibition of the formation of pepsin and acid-pepsin complex (13). They also cause a transient increase in LES pressure. Antacids, which are taken as needed, provide fast symptomatic relief to approximately 50% of patients with mild heartburn (16,17). Although there is rapid onset of relief with antacids, heartburn may return in as little as 30 to 60 minutes, resulting in the need for frequent dosing.

H₂RAs such as cimetidine, famotidine, nizatidine, and ranitidine suppress acid secretion by blocking histamine from binding to the H₂ receptor on the parietal cell (18). H₂RAs only partially inhibit acid secretion elicited by gastrin (which stimulates secretion of histamine by enterochromaffinlike cells) and are therefore more effective at reducing basal acid secretion than at reducing food-stimulated acid secretion (11,15). H₂RAs reduce H⁺ concentration, gastric juice volume, and pepsin production, but they have no effect on LES pressure, gastric emptying, or pancreatic secretion (18). H₂RAs provide relief to approximately 60% of patients (19). Symptomatic relief usually occurs within 30 to 60 minutes and lasts up to 10 hours (19). Some patients, however, may develop tolerance to H₂RAs with continued use (20).
bowel function, causing constipation and diarrhea, respectively (11). The most common side effects of treatment with H2RAs are diarrhea, headache, nausea, and abdominal pain, all of which occur at the same frequency as with placebo. Adverse effects such as gynecomastia and impotence have been associated with the use of cimetidine (12). Side effects are uncommon with PPIs, occurring no more frequently than with placebo. They include diarrhea, headache, nausea, and abdominal pain. PPIs are well tolerated during short- and long-term treatment, and patients rarely discontinue use (22). Because of their superior efficacy and safety profiles, PPIs would be appropriate for over-the-counter use in patient self-management of frequent heartburn (4).

Drug Interactions

By raising intragastric pH, antacids decrease absorption of coadministered drugs that are weak bases, resulting in lower serum levels of these types of drugs. Among the H2RAs, cimetidine can inhibit hepatic metabolism (and, thus, delay clearance) of coadministered drugs, thereby increasing their blood levels. Cimetidine has the potential for clinically significant interactions with, among others, warfarin, theophylline, phenytoin, and diazepam (11). PPIs also reduce gastric acidity and inhibit cytochrome P450 enzymes to some degree. Slight increases in serum warfarin, diazepam, and phenytoin levels may be seen with concomitant omeprazole therapy, and a modest increase in the clearance of theophylline is observed with concomitant lansoprazole therapy (23). Most drug interactions with PPIs, however, have no clinical significance for the majority of patients (23). PPIs are routinely used concomitantly with other medications, such as oral contraceptives and drugs used to treat hypertension, arthritis, and angina, without incident (24). Because warfarin and phenytoin are characterized as having narrow therapeutic windows, patients on these 2 drugs should inform their physicians if they are taking concomitant PPIs.

Table 4
Tips To Help Minimize Heartburn Symptoms

- Eat several small meals instead of 3 large meals per day
- Wait at least 2 hours after meals before lying down
- Avoid the following foods:
  - Coffee and tea
  - Tomatoes and tomato juice/sauce
  - Citrus juice and fruits
  - Carbonated beverages
  - Fatty/fried foods
  - Chocolate
  - Peppermint/spearmint
  - Alcoholic beverages
- Don’t smoke
- Wear loose clothing
- Elevate the head of your bed 6 to 9 inches
- Take your medication as needed to control symptoms

LONG-TERM SAFETY OF PPIs

Initial concerns about long-term use of PPIs included atrophic gastritis; intestinal metaplasia/gastric cancer; bacterial overgrowth; and malabsorption of fats, minerals, and essential nutrients. Since the approval of the first PPI in the United States in 1989, the long-term use of PPIs has been documented as safe, with no conclusive evidence that long-term PPI therapy contributes to the development of atrophic gastritis or intestinal metaplasia/gastric cancer (25–27). As with H2RAs, the use of PPIs has been associated with gastric and duodenal bacterial overgrowth, but the clinical consequence of this has not been established (28). Additionally, the malabsorption of fats and minerals, such as iron, calcium, phosphorus, magnesium, and zinc, does not occur with PPI therapy (24,29,30). Decreased vitamin B12 levels with prolonged PPI therapy have been observed in rare cases (24).

COUNSELING PATIENTS AND REINFORCING THE BENEFITS OF ADHERENCE TO THERAPY

It is widely recognized that PPIs are effective, safe, and cost-effective for controlling heartburn (22,23,31). PPIs would be the appropriate first step in an approach to self-treatment for individuals with symptoms of frequent heartburn typical of uncomplicated GERD (31,32). The success of such a program would depend in large part on patients’ prompt and regular use of medication, adoption of appropriate lifestyle modifications (Table 4), and understanding of when they should seek medical advice.

Studies indicate that patient education and counseling contribute a great deal to treatment adherence and success (33,34). Indeed, patients in clinical trials seem to do better than the general population of patients because they receive counseling and take their medications regularly. Patients who understand their symptoms and treatment tend to feel empowered and invested in success (Table 5) (21,35).

Physicians should educate their patients about the basic mechanism of frequent heartburn (21), the fact that acid-suppressing treatment is available, the ramifications of not treating heartburn, and the importance of making the lifestyle adjustments listed in Table 4. It is important that patients be aware that they should consult their physicians if they do not achieve relief within the allotted treatment period for the medication they are using or if they notice alarm symptoms (such as those listed in Table 1) or other unusual symptoms due to extraesophageal manifestations of GERD (Table 6) (4,19,36).

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CONCLUSION

Familiarity with the mechanism of acid production/secretion and the pathophysiology of heartburn gives physicians the means to understand the mechanism of action and clinical efficacy of each treatment option. Awareness of the differences between the various acid-reducing agents enables physicians to select the best treatment for patients suffering from heartburn. PPIs provide superior relief of frequent heartburn symptoms and have excellent safety profiles. Counseling and reinforcing the benefits of this therapy can improve patient adherence and, consequently, lead to successful management of heartburn.

References


