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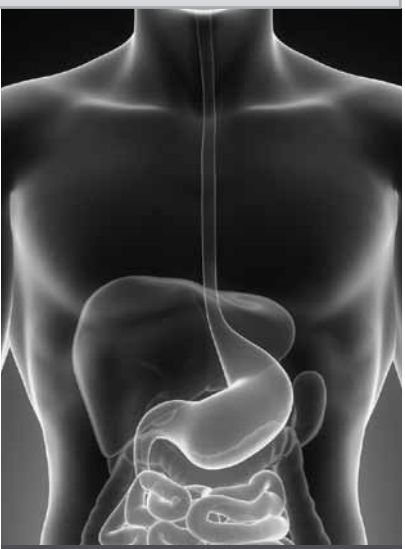

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optimizing over-the-counter management of heartburn

Heartburn is an extremely prevalent condition, affecting 44% to 60% of all Americans at least once monthly, nearly 30% two or more days per week, and up to 7% daily.[1-3] Indeed, more than 50 million Americans are believed to experience the condition of frequent heartburn, defined as occurring at least 2 days a week.[2] For these millions of heartburn sufferers, the availability of over-the-counter (OTC) heartburn medications offers the potential for effective patient-directed management and substantial symptom improvement when used appropriately.

This publication features the input of Philip O. Katz, MD, Chairman of the Division of Gastroenterology at Albert Einstein Medical Center in Philadelphia, Pennsylvania. Dr. Katz is a practicing clinician with active teaching and editorial positions, and is recognized as a national authority on esophageal disease. Dr. Katz is a past president of the American College of Gastroenterology (ACG, 2009-2010) and is a member of the American Gastroenterological Association. He has contributed to the publication of over 150 peer-reviewed papers, as well as numerous abstracts, books, book chapters, and monographs.

overview

Self-management options for patients with heartburn include lifestyle modifications and OTC medications. Lifestyle modifications often recommended in patients with heartburn include dietary changes, losing weight, elevating the head of the bed, avoiding late evening meals, and smoking cessation.[2,4] While these modifications may benefit some patients with frequent heartburn, these changes alone are unlikely to control symptoms in the majority of patients.[5] Further, although some patients may find specific dietary modifications helpful (eg, avoiding caffeine, chocolate, fats), data supporting their clinical efficacy in reducing heartburn are lacking.[2,4]

Over the past 15 years, treatment algorithms for heartburn have expanded to include multiple prescription and OTC options, with a variety of OTC medications currently available for consumers. The ACG guidelines on gastroesophageal reflux disease (GERD) management consider these agents as appropriate options for patient-directed therapy for heartburn.[4] While antacids have been available OTC for decades, OTC histamine$_2$-receptor antagonists (H_2RAs) became available in the mid-1990s. All four prescription H_2RAs are now available in OTC doses that have been shown to decrease gastric acid[4,5] **(Table 1)**. With the switch of omeprazole from prescription-only status in 2003 (omeprazole magnesium Prilosec OTC®),[5] proton pump inhibitors (PPIs) became available OTC. Since the publication of the ACG guidelines,[4] OTC versions of other PPIs have become available (lansoprazole [Prevacid® 24HR], and omeprazole/sodium bicarbonate [Zegerid OTC™]).

Table 1. OTC H_2RA and PPI Medications[5]

H_2RA	Year Approved	PPI	Year Approved
Tagamet HB 200® Cimetidine 200 mg	1995	**Prilosec OTC®** Omeprazole magnesium 20.6 mg	2003
Zantac 75®, Zantac 150® Rantidine 75, 150 mg	1995 (75 mg), 2004 (150 mg)	**Prevacid® 24HR** Lansoprazole 15 mg	2009
Pepcid® AC® Famotidine 10, 20 mg	1995	**Zegerid OTC™** Omeprazole 20 mg with sodium bicarbonate 1110 mg*	2009
Axid® AR Nizatidine 75 mg	1996		

*Must be dosed at least 60 minutes prior to a meal

heartburn treatments work differently

Although all OTC heartburn therapies may provide potential benefit by reducing or neutralizing stomach acid when taken intermittently on an as-needed basis, there are important differences among the available therapies. Antacids dissolve in gastric acid, releasing anions that partially neutralize existing gastric acid in the stomach **(Figure 1)**.[6,7] While they act rapidly, they have a short duration of effect, with neutralizing effects typically lasting from 20 to 60 minutes in fasting subjects and up to 3 hours when taken after a meal.[6]

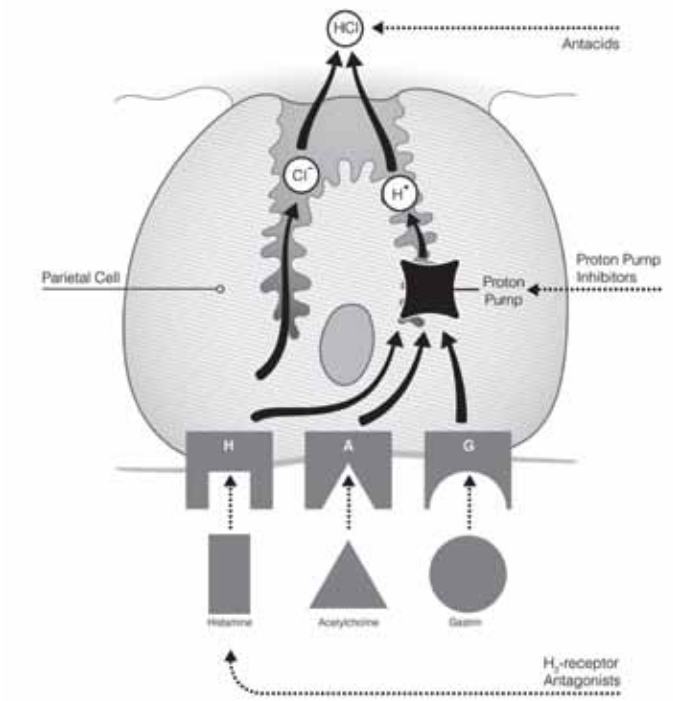

Figure 1. Production of acid in the parietal cells in the stomach.[7]

Johnson LR. Gastric Secretion. In: Barrett K, ed. *Gastrointestinal Physiology*. Newark, De: The McGraw Hill Companies; 2006:75-94. Reproduced with permission of The McGraw-Hill Companies.

H_2RAs slow acid secretion by competitively and reversibly binding to the H_2 receptors on the parietal cells.[8] These agents act quickly, with gastric pH increasing within 30 minutes of taking a dose and persisting for up to 10 hours.[4] Increasing evidence suggests that when H_2RAs are taken multiple days in a row, at consistent times of the day, they exhibit tachyphylaxis—declining gastric acid control.[9-18]

Miner et al. compared the durability of acid suppression achieved with OTC doses of famotidine and omeprazole magnesium in a randomized, double-blind, 3-period crossover study involving 31 healthy adults.[10] In this study, for each assessment after Day 1, omeprazole magnesium 20.6 mg showed significantly greater gastric acid suppression with continued usage for 14 days, while acid suppression with famotidine 10 mg and 20 mg declined over time **(Figure 2)**.[11]

While the mechanism for this phenomenon remains speculative, it may involve the up-regulation of parietal cell receptors for other mediators of acid secretion (ie, acetylcholine, gastrin), the sensitization of H_2 receptors, and/or an alteration in receptor turnover after chronic competitive inhibition.[16,17]

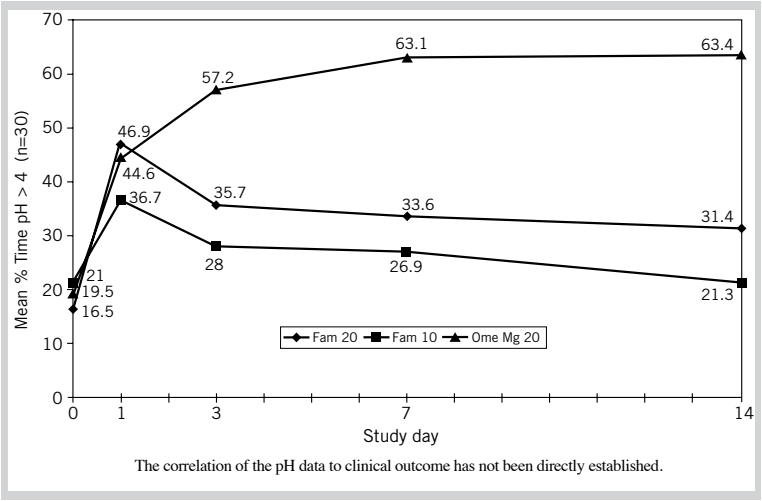

Figure 2. Mean percentage time gastric pH > 4 across 14 days[10]

Miner, PB, Allgood. LD, Grender, JM. Comparision of gastric pH with omeprazole magnesium 20.6 mg (Prilosec OTC) o.m. famotidine 10 mg (Pepcid AC) b.d. and famotidine 20 mg b.d. over 14 days of treatment. *Aliment Pharmacol Ther.* 2006; 25:103-109. Reprinted with permission from John Wiley & Sons, Ltd., Publisher 8/4/11.

Commenting on these data, Dr. Katz added that "there is no change in acid control with PPIs over time, as far as we know. However, there is a potential reduction in acid control with H_2RAs, and therefore the possibility patients may not maintain the same symptom relief with frequent H_2RAs." He continued to qualify these observations, however, noting that despite the common belief that "there ought to be a connection between acid control and symptom relief, this connection has not been conclusively shown."

PPIs suppress acid production by inhibiting the H+/K+ ATPase enzyme system (proton pump) at the secretory surface of the gastric parietal cell.[8,19,20] Because PPIs inhibit only actively-secreting proton pumps, the ability of the parietal cell to secrete acid is restored when new pumps are converted from their inactive status.[8,21,22] Thus, PPIs do not completely inhibit acid secretion, with a single dose believed to inhibit 70% to 80% of active pumps.[8,21,22] Nevertheless, because the proton pump is the final common pathway for acid secretion, PPIs inhibit gastric acid secretion by all known stimuli and are more potent than agents targeting parietal cell receptors.[8,22] The effect of PPIs on intragastric acidity depends strongly on dose, while the onset of action depends on the bioavailability of the agent (typically 1-2 hours).[8,19,20] Despite their short half-lives, PPIs achieve prolonged acid inhibition, with full restoration of acid secretion generally occurring 72 hours after the last dose.[8,19,20]

practical considerations for use of otc heartburn medications

Choosing a heartburn medication

Both antacids and OTC H_2RAs are appropriate for on-demand therapy when rapid relief of episodic heartburn is desired.[23-26] The OTC H_2RAs can also be useful for preventing symptoms that are associated with eating food or drinking beverages that cause heartburn.[25,26] Both types of therapies are indicated for a maximum of 14 days of therapy, after which consumers with persisting symptoms should seek advice from a physician.[23-26] Despite some differences in potency, duration, drug interaction potential, and onset of action, the H_2RAs can generally be used interchangeably.[4]

The OTC PPIs are indicated to treat frequent heartburn (occurring 2 more days weekly), and are intended for once daily use every day for 14 days, with a repeat 14-day course every 4 months if needed.[27-29] As with antacids and OTC H_2RAs, consumers with symptoms persisting beyond 14 days are encouraged to consult a physician.

Omeprazole magnesium and lansoprazole were each studied in a pair of randomized, double-blind, placebo-controlled studies investigating OTC PPI dosing regimens in subjects with frequent heartburn.[30-31] Both drugs were shown to eliminate heartburn in half of the subjects during Day 1 of treatment. Across 14 days of this OTC regimen, subjects who received lansoprazole were heartburn-free on 59.9% and 64.7% of 24-hour days in studies 1 and 2, respectively; both rates were statistically significant versus placebo.[30] Similarly, subjects who received omeprazole magnesium were heartburn-free on 64.4% and 67.8% of 24-hour days in studies 1 and 2, respectively; this was also statistically significant versus placebo.[31]

The effects of marketed PPIs on intragastric pH have been well studied.[10,32-35] Recent studies have also investigated the effect of OTC doses of 2 of the available OTC PPIs on intragastric pH. In a randomized, controlled study of the available OTC doses of two marketed OTC PPIs, the mean time gastric pH > 4 was found to be 24% greater among patients taking omeprazole magnesium 20.6 mg than lansoprazole 15 mg.[36] In another study conducted by Miner et al., omeprazole magnesium 20.6 mg given once in the morning provided significantly greater gastric acid suppression ($P < 0.001$) than famotidine 10 mg twice daily or 20 mg twice daily.[10] Despite these findings, however, the available data are too limited to draw conclusions regarding the relationship between acid suppression and symptom relief, and well-designed, long-term outcome studies are needed to establish the link between heartburn symptom scores and 24-hour gastric pH profiles.[37]

Safety considerations

OTC heartburn medications are well-tolerated and their safety has been well-established.[38] The potential for drug interactions with these agents should be appreciated. This is especially true of antacids, that can bind or chelate a number of drugs, including tetracyclines, quinolone antibiotics, bisphosphonates, and iron salts.[6] Additionally, it is theoretically possible that any drug that raises gastric pH—including antacids, H_2RAs, or PPIs—can alter the absorption of drugs with pH-dependent absorption (eg, ketoconazole).[27,39] Further, given the potential for omeprazole magnesium and lansoprazole to interfere with CYP2C19 and other cytochrome P450 enzymes, OTC PPI labels warn of a number of potential interactions, including digoxin, warfarin, tacrolimus, cilostazol and ataznavir.[27-29] In addition, the Food and Drug Administration (FDA) has required that the labels of OTC and prescription products containing omeprazole or omeprazole magnesium reflect a warning regarding the potential for omeprazole to decrease levels of the active metabolite of clopidogrel, potentially reducing its antiplatelet effects.[40] Patients using clopidogrel should consult with their health care providers if they are taking omeprazole, including Prilosec OTC®.[40]

Other safety considerations for OTC heartburn medications include the need for caution with sodium bicarbonate-containing antacids[24] and with Zegerid OTC™[28] in patients with conditions requiring sodium restriction. Recent FDA warnings regarding an increased risk of osteoporotic fractures with high doses of prescription PPIs have not been extended to OTC PPIs.[41] The relevance of other safety concerns with prescription PPI use, such as an increased risk of hypomagnesemia and *Clostridium difficile* infection,[38,42-44] have not been characterized with respect to OTC doses. However, FDA recently added the following wording to all OTC PPI labeling: "Stop use and ask a doctor if you get diarrhea." A similar warning will appear on prescription PPI labeling.

Are heartburn sufferers getting optimal relief?

Results of a 2000 survey of 1,000 patients experiencing heartburn at least once a week indicated that only 29% of patients taking OTC medications for their symptoms were completely satisfied with their therapy.[45] At the time, only antacids and H_2RAs were available OTC. More recently, however, a survey conducted after the introduction of OTC omeprazole magnesium indicated that 94% of patients who take OTC heartburn medications (antacids, H_2RAs, or PPIs) are satisfied with their treatment.[46] Current data estimate that approximately 8 million people use H_2RAs at least twice weekly.[3] Interestingly, a study involving 758 self-reported heartburn sufferers in an OTC setting indicated that 35% of patients using OTC omeprazole magnesium had never consulted a physician about their heartburn before the study.[47] These findings underscore the opportunity for consumer education regarding the treatment of heartburn, including how to optimize management with OTC medications (eg, daily use PPIs for frequent heartburn for up to 14 days, on-demand use of H_2RAs for episodic heartburn for up to 14 days) and when to speak to a health care provider.

Optimizing efficacy and safety

Health care providers educating patients regarding the use of OTC heartburn medications should appreciate the following key recommendations for optimizing the efficacy and safety of these agents:

- PPIs should be dosed 30 minutes before breakfast in order to achieve optimal antisecretory efficacy.[4,48] Zegerid OTC™ must be dosed at least 60 minutes prior to a meal to prevent degradation of the drug.[28]
- When H_2RAs are taken multiple days in a row, at consistent times of the day, they exhibit tachyphylaxis-declining gastric acid control.[9-18]
- Patients should not use any OTC heartburn medication beyond their 14-day indication unless otherwise directed by their physician since some may be at risk for more serious complications of GERD.[4] Patients whose symptoms do not improve within 14 days of self-medicating with these agents should consult their health care provider.
- Patients with alarm symptoms of complications (eg, dysphagia, odynophagia, bleeding, weight loss, anemia)[4] or other serious symptoms (eg, chest pain, nausea, vomiting) should consult their health care provider.

"Patients should be encouraged to consult their physician if they're using these drugs in any way not in concert with the label." - Philip Katz, MD

conclusions

Heartburn is extremely common in the American population, affecting more than 50 million Americans twice weekly.[2] The availability of OTC heartburn medications allows for effective patient-directed management and can lead to significant improvement for heartburn sufferers. However, optimum self-management requires that patients use OTC medications appropriately. Patients should understand that antacids and OTC H_2RAs may be useful for episodic heartburn, while OTC PPIs are intended for frequent heartburn. When H_2RAs are taken multiple days in a row, at consistent times of the day, they exhibit tachyphylaxis-declining gastric acid control.

Patients using OTC heartburn medications beyond the 14-day indication should be referred for further evaluation in order to rule out gastrointestinal pathology (or other serious conditions), and to assess the need for other therapies.

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