Proton Pump Inhibitor Clinical Trials: Focus On Lansoprazole In The Treatment Of Gastroesophageal Reflux Disease And Frequent Heartburn

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Abstract

Purpose: Heartburn is a common symptom among adults, and can be troublesome when experienced more than two times a week. Heartburn and regurgitation are characteristic symptoms of gastroesophageal reflux disease, and may be experienced alone or in combination with other symptoms of reflux. The nurse practitioner should be aware of recent developments in the management of frequent heartburn that may be relevant to patients with this condition. Therefore the present review discusses the current treatment options for frequent heartburn with a focus on lansoprazole 15 mg, a recently approved over-the-counter proton pump inhibitor for frequent heartburn. Methods: The role of lansoprazole in the treatment of gastroesophageal reflux disease and heartburn was assessed using an online database search using PubMed, supplemented by the author’s knowledge of the management of the disease. Conclusions: The management of frequent heartburn is an important issue for nurse practitioners. Available pharmacologic treatments include antacids, histamine2-receptor antagonists, and proton pump inhibitors. Lansoprazole has recently been approved for over-the-counter sale for the short-term (14 days) treatment of frequent heartburn. Implications for practice: Nurse practitioners should be aware of the evidence to support the change in status of lansoprazole from prescription to over-the-counter, in order to appropriately advise their patients.

INTRODUCTION

According to the Montreal Global Consensus Group, gastroesophageal reflux disease (GERD) is “a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications” [1]. This definition has recently been adopted by the American Gastroenterological Association (AGA) [2]. Heartburn and regurgitation are characteristic symptoms of GERD, and are defined by the Montreal Group as “a burning sensation in the retrosternal area” and “the perception of flow of refluxed gastric content into the mouth or hypopharynx,” respectively [1]. The burning sensation associated with heartburn has also been described as rising from the stomach or chest area and extending to the neck, throat, and in some cases, the back [3]. Heartburn is considered frequent when symptoms occur during two or more days per week [4]. However, patients will often describe their symptoms in different ways, so the nurse practitioner (NP) should carefully consider how the published definition applies to their practice.

Heartburn is a very common complaint in the adult population in the United States (US), experienced by more than one-third of people one or more times per month and by 25 million on a daily basis [5]. Common risk factors include spicy or greasy foods, stress, alcohol, smoking, overeating, lying down too soon after eating, wearing tight clothing, and pregnancy [3, 5, 6]. The influence of age on the frequency of heartburn requires further study, but as patients age they may be at greater risk of esophagitis [3]. Obesity, male gender, and genetics may also play a role in some patients [3]. Heartburn that occurs at night has particularly important consequences for the patient, as this symptom can affect the quality of sleep and can impair performance during the day after a nighttime episode [7].

The purpose of this review, prepared using the results of PubMed literature searches supplemented by the author’s clinical experience, is to provide an overview of the pathophysiology and management of gastric acidic disorders, to discuss role of the proton pump inhibitor (PPI)
lansoprazole for its approved indications, and to place this information into a perspective that is useful for the nurse practitioner (NP). A secondary objective is to present evidence that the over-the-counter (OTC) availability of lansoprazole 15 mg provides an effective and well tolerated choice for the management of frequent heartburn in a self-treating population seeking the advice of an NP. This review focuses on lansoprazole 15 mg, which is one of the more recently approved over-the-counter proton pump inhibitor (PPI) for frequent heartburn. The omeprazole 20 mg/sodium bicarbonate 1100 mg combination product is another over-the-counter option recently approved for treating frequent heartburn. However, to date no clinical data is available for this drug.

DIFFERENTIAL DIAGNOSIS

Although the perceived level of discomfort may vary, even mild gastrointestinal symptoms occurring on two or more days per week are often considered troublesome by patients, according to population-based studies [1]. While many patients will complain of typical symptoms of heartburn, others may present with symptoms that are respiratory, nasopharyngeal, or cardiac in origin [8]. Cardiac symptoms require careful assessment to rule out cardiac pathology [9]. The presence of alarm symptoms, which include bleeding from any part of the gastrointestinal tract, difficulty swallowing, choking, unexplained weight loss, or anemia, mandate a full diagnostic work-up by a gastrointestinal specialist, including endoscopy, to ensure that more serious complications have been ruled out [8]. Patients may experience chronic cough, laryngitis, and asthma that is directly or indirectly associated with GERD; however, GERD is rarely the sole cause of such symptoms. If heartburn or regurgitation is absent, unexplained asthma and laryngitis symptoms are probably not related to GERD [1].

PATHOPHYSIOLOGY OF ACID-RELATED GASTROINTESTINAL DISORDERS

In the stomach, gastric acid is produced by the parietal cells located in the lining of the stomach through the action of H⁺/K⁺-ATPase, known as the gastric proton pump [10]. Regulation of stomach pH is a complex process that includes stimulation by gastrin, histamine, and acetylcholine (Figure 1) [10-12]. Secretion of gastric acid is evoked by a number of physiologic stimuli, including the presence of food in the stomach or intestines, or merely the taste, smell, or thought of food [10-12].
intermittent antireflux medication can improve quality of life and may regress GERD in response to treatment with these modalities [13-16]. For example, in one clinical study, symptoms of GERD remained improved after six months in 80.2% and 77.8% of patients who had been randomly assigned to continuous (n=658) and on demand (n=634), respectively following four weeks of daily medication. In this same study, the proportion of patients who were completely/very satisfied with treatment after six months were 82.2% for continuous medication and 75.4% for on demand. In addition, quality of life scores were also maintained during on demand therapy [14].

CURRENT TREATMENT OPTIONS
NONPHARMACOLOGIC APPROACHES

Risk factors associated with the development of reflux disease may be categorized into four broad groups: genetic, demographic, behavioral (i.e., lifestyle), and those associated with comorbidity [17]. While these factors indicate that NPs might be able to influence the outcomes of frequent heartburn by providing lifestyle counseling, the evidence supporting the effectiveness of individual lifestyle interventions is somewhat limited and may not apply to all patients (Table 1) [2, 9].

PHARMACOLOGIC TREATMENT

The three major classes of drugs used to treat GERD are antacids, histamine-2-receptor antagonists (H$_2$RAs), and PPIs. The mechanism and efficacy of each class are summarized in Table 2, and the sites of action of H$_2$RAs and PPIs are shown in Figure 1. A recent meta-analysis showed that in patients with esophagitis, the rank order of esophageal healing rates for each drug class was as follows: PPIs (83%), H$_2$RAs (52%), placebo (18%); antacids were used as rescue medication [21, 22].
effective in treating symptomatic GERD [4, 23]. Unlike H2RAs and PPIs, antacids do not prevent acid secretion, and thus do not treat the cause of heartburn. Results from a study that included 155 subjects with heartburn for an average of 11 years, 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 indicated that long-term antacid use may mask significant health issues. [25]. Endoscopy revealed hiatal hernia in 57% of subjects, erosive esophagitis in 47% of subjects, and nondysplastic Barrett’s esophagus in 6% of subjects. The authors of this report suggested that heartburn over long periods warrants a full medical evaluation to determine appropriate treatment. Nurse practitioners should caution patients who are taking antacids for their heartburn to consult their pharmacist for guidance on possible drug interactions.

HISTAMINE-RECEPTOR ANTAGONISTS

H2RAs are best used preventatively (e.g., before a large meal, before eating late at night, or before exercise) [3]. Over-the-counter H2RA preparations may not be suitable as universal therapies; studies have suggested that complete symptom relief may occur in as few as 15% of patients [26]. The most common adverse events include headache, dizziness, diarrhea, fatigue and confusion [21]. Patients with frequent heartburn will probably require treatment that is more effective than H2RAs, although this class of drug remains appropriate for episodic heartburn [4]. Tolerance has been shown to develop in patients who test negative for Helicobacter (H) pylori [27].

PROTON PUMP INHIBITORS

PPIs have been available for the treatment of GERD symptoms, including heartburn, since the late 1980s [28]. PPIs currently available on prescription are dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. The recently-published AGA Technical Review on the Management of Gastroesophageal Reflux Disease reports that “the current consensus is that empirical PPI therapy is appropriate for uncomplicated heartburn” [2]. PPIs significantly reduce gastric acid secretion throughout the 24-hour dose interval, maintaining a gastric pH of four or greater than four for 15-21 hours, in contrast to H2RAs, which maintain efficacy for about eight hours [3]. Although individual response to treatment for heartburn may vary, PPIs have superior efficacy compared with H2RAs and antacids [2, 21]. Among the abundant clinical trial data available on PPIs, no major differences in efficacy between different PPIs have been noted [2, 21]. Lansoprazole 15 mg was approved for nonprescription use for the 14-day treatment of frequent heartburn in May 2009, and omeprazole 20 mg has been available without a prescription since 2003 for the same indication. The most frequent adverse events associated with the use of PPIs are headache, diarrhea, constipation, and abdominal pain [21]. Some data suggest that other risks, albeit relatively rare, of long-term high-dose treatment, including hip fracture, infectious gastroenteritis and Clostridium difficile colitis, community-acquired pneumonia, and decreased cyanocobalamin (vitamin B12) absorption [21, 28-31]. Most of these data come from observational studies [28], which tend to produce data that are confounded by the existence of comorbidities, concomitant medications, and lifestyle factors in the populations examined [21, 28, 30, 31]. The mechanisms of these risks are not fully understood, but may be related to the reduction in gastric acidity that may reduce, for example, the release of calcium from dietary intake [28]. Overall, the benefits of PPI treatment exceed the risks, although NPs should monitor patients and advise them accordingly.

Drug interactions have been reported with PPIs, but many of these are not clinically significant. However, important interactions with omeprazole have been reported with caffeine, several anticonvulsant drugs, diazepam, digoxin, methotrexate and warfarin. Ketoconazole and fluvoxamine have been shown to inhibit the metabolism of omeprazole [32]. An interaction with clopidogrel has been reported for omeprazole in high-risk coronary patients [33-36]; further research is required to fully assess the clinical implications of this finding. Fewer clinically significant drug interactions have been reported with lansoprazole, but interactions with theophylline, clarithromycin, and tacrolimus may occur [32]. Reports of drug interactions with pantoprazole and rabeprazole are limited [32].

To address concerns raised about patients using PPIs appropriately in OTC settings [4], Fendrick and colleagues studied consumers in a real-world setting (five geographically distinct shopping malls in the US) by using self-reported data from people with heartburn [37]. The results showed a high level of patient compliance with PPI usage instructions according to the product labeling, including those recommending the patient seek medical care if symptoms persist, worsen, or recur within a specified time [37]. These recommendations are located on the packaging of OTC medications. The package information also provides
advice to the patient regarding the need for consultation with a primary care provider if symptoms worsen, persist, or return within a short period (4 months).

**LANSOPRAZOLE IN THE TREATMENT OF ACID-RELATED GASTROINTESTINAL DISORDERS**

**EFFICACY OF LANSOPRAZOLE**

Lansoprazole was the second PPI to become commercially available, and is now widely prescribed. Since clinical use began, this agent has proven effective in a wide range of acid-related gastrointestinal disorders [24]: short-term treatment of symptomatic GERD (up to eight weeks), short-term (up to four weeks) treatment and maintenance of healing of duodenal ulcers, risk reduction of nonsteroidal anti-inflammatory drug–associated gastric ulcer, and maintenance of healing of erosive esophagitis. Lansoprazole 30 mg has been shown to be effective in the short-term treatment of benign gastric ulcer and erosive esophagitis and, when used in combination with amoxicillin 1g and clarithromycin 500 mg as part of twice-daily triple therapy, for the eradication of H pylori [24]. A 60-mg dose is approved in the US for the treatment of hypersecretory conditions such as Zollinger-Ellison syndrome [24].

A dose finding study showed that 15, 30, and 60 mg doses of lansoprazole were approximately equally effective for the treatment of duodenal ulcer when used for four weeks, and the benefits were maintained at six months [38]. In nonerosive esophagitis, effects on daytime heartburn were similar with lansoprazole 15 and 30 mg, while the 15-mg dose was more effective against nighttime symptoms [39]. A numerical advantage of lansoprazole 15 mg over 30 mg was shown in a study looking at both daytime and nighttime heartburn [26]. For this reason, the use of lansoprazole 15 mg was tested for the treatment of frequent heartburn in an OTC setting.

Two recently published reports of three multicenter, double-blind, randomized studies, involving almost 2000 subjects, examined the effects of lansoprazole on daytime and nighttime frequent heartburn in self-treating populations [40, 41]. In two studies, published in a single report, adults with frequent heartburn (on two or more days per week for the past month) were randomized to receive lansoprazole 15 mg or placebo for 14 days [40]. In the third study, subjects had to have heartburn on at least two nights per week, and they were randomized to receive lansoprazole 15 mg, lansoprazole 30 mg, or placebo each morning for 14 days [41].

The mean percentage of 24-hour days without heartburn during 14 days of treatment was greater in subjects treated with lansoprazole than in placebo recipients (p<0.0001 vs. placebo for lansoprazole in each study) (Figure 2), with more subjects on lansoprazole reporting no heartburn on day one of treatment compared with placebo (15-mg group vs placebo, p≤0.0005; 30-mg group vs placebo, p=0.0004) [40]. Subjects treated with lansoprazole also experienced a higher mean percentage of nighttimes with no heartburn during the 14-day treatment period, compared with subjects on placebo (p<0.0001 for all doses vs placebo) (Figure 3) [41].
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Figure 4
Figure 2. Percentage of 24-hour days with no heartburn during 14-day, double-blind treatment with lansoprazole 15 mg once daily in the intent-to-treat populations of studies 1, 2 (*p<0.0001 for lansoprazole 15 mg vs placebo) and 3 (*p<0.0001 for lansoprazole [15 and 30 mg] vs placebo). : (A) Reprinted by permission from Kushner et al. (2009) [40]. is a registered trademark of JTE Multimedia, LLC, 1235 Westlakes Drive, Suite 220, Berwyn, PA (610) 889-3730. (B) Reprinted from Peura et al. (2009) [41].

Figure 5
Figure 3. Percentage of nighttimes with no heartburn during 14-day, double-blind treatment with lansoprazole 15 mg or 30 mg once daily in the intent-to-treat population. *p<0.0001 for lansoprazole 15 mg vs placebo, and for lansoprazole 30 mg vs placebo. : Reprinted from Peura et al. (2009) [41].

The results from these studies show that, compared with placebo, lansoprazole 15 mg and 30 mg are both efficacious for the treatment of frequent heartburn. The AGA recommends that for patients on maintenance therapy, the lowest effective dose should be used [9]; dose reduction should be considered in patients started on higher lansoprazole doses (e.g., 30 mg) and may be preferable to changing to an H\textsubscript{2}RA [42, 43].

SAFETY OF LANSOPRAZOLE
The tolerability of lansoprazole has been evaluated in more than 30,000 patients in clinical trials [24]. The most frequent adverse events observed with lansoprazole as monotherapy are those noted for PPIs as a class, namely diarrhea, nausea, headache, and abdominal pain [24]. These events were observed in ≤5% of patients in placebo-controlled, 4-week to 12-week lansoprazole studies in the US [24]. Dose-response data indicate that the incidence of diarrhea is dose-dependent, remaining at 5% or less with lansoprazole doses up to 30 mg [24]. In general, adverse events experienced by patients on lansoprazole 15 mg and 30 mg are mild and transient [40, 41].

PLACE OF LANSOPRAZOLE IN THE MANAGEMENT OF HEARTBURN
If the presence of alarm or cardiac symptoms has been ruled out, the first line of treatment for uncomplicated heartburn should be lifestyle modification, although almost all of the suggested modifications have not been supported by in well-designed, randomized, controlled studies [9] [44].
For patients who do not respond to lifestyle modifications, lansoprazole is a useful and well-tolerated option in the treatment of acid-related gastrointestinal disorders (Table 3). Results from three studies described demonstrated that once-daily lansoprazole 15 mg was effective and had a good tolerability profile in the treatment of frequent, including nighttime, heartburn in a self-treating population.[40, 41] The 15-mg dose of lansoprazole, the lowest effective dose for acid-related gastrointestinal disorder symptoms, was shown to be as effective as the 30-mg dose.[41].

**Figure 6**
Table 3 FDA-Approved Indications for Use of Lansoprazole in Adults

<table>
<thead>
<tr>
<th>Indication</th>
<th>Lansoprazole (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic GERD</td>
<td>15 mg once daily for up to 8 weeks</td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>30 mg once daily for up to 8 weeks (short-term treatment)</td>
</tr>
<tr>
<td>NSAID-associated gastric ulcer</td>
<td>15 mg once daily (maintenance dose)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>15 mg once daily for 4 weeks (short-term treatment)</td>
</tr>
<tr>
<td>Benign gastric ulcer</td>
<td>80 mg once daily for up to 8 weeks</td>
</tr>
<tr>
<td>Achalasia/pyloric stenosis</td>
<td>30 mg twice daily for 10 to 14 days (triple therapy)</td>
</tr>
<tr>
<td>Pathological hypersecretory (i.e., Zollinger-Ellison)</td>
<td>60 mg once daily</td>
</tr>
</tbody>
</table>

For patients who do not respond to treatment with lifestyle modification and a 14-day course of lansoprazole 15 mg one hour before breakfast, further investigation of the cause of their heartburn is warranted. Additional treatments will be based on the results of the investigation.

**CONCLUSIONS**
Heartburn is very common among the adult US population, and is one of the symptoms characteristic of GERD. Untreated heartburn has a negative impact on the quality of life of affected people and may, in some patients, lead to the development of serious sequelae such as Barrett’s esophagus and esophageal cancer. Nurse practitioners are ideally placed to guide patients who complain of heartburn symptoms to the most effective treatment. Based on clear therapeutic benefits with few adverse events, PPIs are considered the treatment of choice for frequent heartburn (occurring two or more times per week). Lansoprazole has a clearly established efficacy and safety record, offering people with frequent heartburn an appropriate option for initial treatment. The availability of lansoprazole OTC gives patients another choice for their treatment.

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