PHARMACY REVIEW

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GERD Management: The Case for Lifestyle in an Era of PPIs

Abstract: *Gastroesophageal reflux disease (GERD) is a common condition in the United States, routinely treated with proton pump inhibitors (PPIs). While effective and generally well tolerated, PPIs have been associated with undesirable long-term side effects and are often used inappropriately. Lifestyle medicine can be effective in reducing GERD symptoms in many patients without the untoward side effects of pharmacotherapy. This article will describe relevant emerging and established side effects of long-term PPI use, the efficacy of lifestyle modifications in the management of GERD, and discuss the importance of advocating for lifestyle when PPIs are not otherwise indicated.*

Keywords: proton pump inhibitor; GERD; dementia; chronic kidney disease; bone fracture; lifestyle

Gastroesophageal reflux disease (GERD) is a common condition in the United States, with estimated prevalence between 18.1% and 27.8%.[1] Proton pump inhibitors (PPIs) are routinely used to treat GERD and rank among the top prescribed drug classes for Medicare patients.[2,3] While PPIs are very effective at reducing GERD symptoms and are generally well tolerated, their use has been associated with undesirable long-term effects.

Proton pump inhibitor therapy is indicated for short-term use in the treatment of mild, uncomplicated GERD. The 2013 American College of Gastroenterology (ACG) guidelines recommend an 8-week course of PPI therapy for reflux symptom relief.[4] PPIs are also available over the counter for self-care treatment of GERD. The manufacturer labeling instructs a 2-week course of therapy once every 4 months unless directed otherwise by a physician.[5] While both recommendations are time limited, in practice, PPIs are often used as chronic medications for extended intervals.

Although lifestyle modifications can be an effective treatment for many cases of GERD, the concept of an "easy fix" with pharmacotherapy may be more appealing to patients who suffer from the condition. Many of these patients may be unaware of the potential long-term effects and consider therapy with this class of medications as benign. Because of the widespread use of PPIs (both under medical supervision as well as self-care), it is important for health care professionals to be aware of and educate patients regarding the possible long-term effects of these medications and to provide alternatives to pharmacotherapy for appropriate patients.[6] This article will discuss relevant established or emerging adverse effects associated with long-term PPI use, the efficacy of lifestyle modifications in the management of GERD, and the importance of advocating for lifestyle when PPIs are not otherwise indicated.

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Emerging Potential Adverse Effects Associated With Long-Term PPI Use

Dementia

Recent attention has been drawn to the potential increase in incident dementia associated with PPI use in the elderly.

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The mechanism by which this occurs has not been fully elucidated, but several theories exist. One theory contributes the cognitive decline to the PPI's (specifically lansoprazole and omeprazole) ability to cross the blood-brain barrier and directly affect the brain through modulation of enzymatic activity.[7] Another possible explanation is based on the association of PPIs with low vitamin B_{11} levels, a deficiency known to affect cognition and neural pathways.[8] To date, 3 studies have evaluated the correlation between PPI use and dementia with inconsistent results.[9-11]

The first study, conducted by Haenisch et al, was a 6-year longitudinal evaluation of 3076 dementia-free, community-dwelling patients age 75 and older.[9] The patients were followed for four, 18-month intervals to determine the association between the use of PPIs and the risk of incident dementia. Neuropsychological assessments for diagnosis of dementia were completed every 18 months throughout the study. A total of 713 patients (23.2%) received a PPI during the study period. PPI use was defined as patient-reported use of a PPI at baseline and/or use at one of the 18-month follow-ups. Results found the use of PPIs was associated with an increased risk of dementia (hazard ratio [HR] = 1.38; 95% confidence interval [CI] = 1.04-1.83; P = .02).

A prospective cohort study conducted by Gomm et al evaluated PPI use and incident dementia in 73 679 patients over the course of 7 years.[10] The patients, age 75 and older, had no dementia at baseline. During the study period, patients were either exposed to regular PPI therapy (defined as at least one PPI prescription every 3 months of an 18-month evaluation interval) or no PPI therapy (defined as no PPI prescriptions in the 18-month evaluation interval). Patients with occasional PPI use (use less than that defined as regular use) were excluded from analysis. Variables associated with the development of dementia were controlled for during analysis. A total of 29 510 patients were diagnosed with dementia during the study, of which 2950 were exposed to regular PPI therapy. The study found the use of PPIs was associated with a significantly increased risk of incident dementia (HR = 1.44; 95% CI = 1.36-1.52; P < .001).

The third study, a case-control evaluation, was conducted to identify risk factors associated with the development of dementia in German primary care patients. A total of 11 956 patients with dementia were matched 1:1 to patients without dementia on the basis of age, sex, health insurance, and physician.[11] The study subjects were mostly women (61.0%), with an average age of 80.4 years. The study found that the use of PPIs was less frequent in dementia patients than in controls (44.3% vs 45.8%, respectively), and the use of PPIs was associated with a decreased risk of developing dementia (HR = 0.94; 95% CI = 0.90-0.97; P = .0008).[11]

Chronic Kidney Disease

Another emerging concern with the long-term use of PPIs is development of chronic kidney disease (CKD). It is thought the development of CKD is mediated by PPI-induced acute kidney injury (in the form of interstitial nephritis) or PPI-induced hypomagnesemia.[12,13]

A retrospective case-control study was conducted to evaluate the risk of incident CKD with the use of PPIs.[14] A total of 76 462 patients were evaluated in the study of which 22 734 used a PPI during the observational period. PPI use was determined by a PPI prescription filled during a quarter of follow-up. A total of 4711 (20.7%) patients using PPI therapy developed CKD during the study compared to 14 600 (27.2%) cases of CKD in non-PPI users. After controlling for factors known to increase CKD risk (age, gender, race, vascular disease, gastrointestinal comorbidities, chronic obstructive pulmonary disease, cancer, diabetes, and hypertension), analyses revealed a statistically significant increase in the risk of CKD among PPI users, odds ratio = 1.10 (95% CI = 1.05-1.16; P < .0001).

The Atherosclerosis Risk in Communities study evaluated the risk of incident CKD associated with PPI use in a population-based cohort study.[15] Incident CKD was observed in 56 of the 332 PPI users (16.9%) compared to 1382 cases (13.6%) in the group of 10 160 nonusers. After adjustment for potential confounders such as demographics, clinical measurements, comorbidities, and concomitant medication use, participants using PPIs had 1.5 times greater risk of developing incident CKD compared to nonusers (95% CI = 1.14-1.96; P = .003).

Established Potential Adverse Effects Associated With Long-Term PPI Use

Bone Loss/Osteoporosis

While the findings associating PPI use with incident dementia and CKD are not concrete, other adverse events such as bone loss and fracture have been more widely reported. Calcium absorption, while dependent on many different factors, is thought to be decreased by the use of PPIs.[16] Another possible mechanism for this observed bone loss is through PPI-mediated hypomagnesemia.[17]

In 2010, the US Food and Drug Administration issued a safety alert implicating PPI use with fractures of the hip, wrist, and spine.[6] This alert was based on high-level evidence supporting bone loss and fracture with long-term exposure. In response to these findings, the Beers Criteria added PPIs to the list of medications to avoid in the geriatric population.[18] Their recommendation specifically states that PPIs should not be used for courses longer than 8 weeks without justification. A recent meta-analysis found that use of PPIs was associated with a 26% increased risk of fracture at the hip (relative risk [RR] = 1.26; 95% CI = 1.16-1.36; P < .0001; I^2 = 71.9%), 58% increased risk of fracture at the spine (RR = 1.58; 95% CI = 1.38-1.82; P = .498; I^2 = 2.38%), and a 33% increased risk of fracture at any site (RR = 1.33; 95% CI = 1.15-1.54; P < .001; I^2 = 66.07%).[19]

Community-Acquired Pneumonia

A second established side effect from long-term PPI use is the increased risk of community-acquired pneumonia. Several mechanisms have been proposed to explain this relationship including an alteration of gut and/or respiratory flora secondary to decreased gastric/respiratory tract acidity.[20,21] A recent systematic review and meta-analysis of 26 studies found that outpatient PPI use is associated with a 1.5-fold increased risk of community-acquired pneumonia (RR = 1.49; 95% CI = 1.16-1.92; I^2 = 99.2%; $P < .001$), with the highest risk occurring during the first 30 days of therapy.[22] The same study found that PPI use was also associated with an increased risk of hospitalization for community-acquired pneumonia.

Nonpharmacologic Treatment of GERD

While many patients turn to pharmacotherapy to treat GERD, lifestyle modifications are also effective in the management of reflux symptoms and esophageal acid exposure. The 2013 ACG guidelines state that lifestyle interventions are part of GERD therapy, and counseling regarding lifestyle changes should be provided to patients with GERD.[4]

To date, weight loss is the only lifestyle modification with supporting evidence from multiple randomized controlled trials (RCTs) in multiple populations.[23] RCTs have shown both reduced reflux symptoms and reduced esophageal acid exposure with weight loss.[23] The decrease in symptoms may be dose-dependent, and one study found symptom improvement in a group with a mean body mass index of only 23.5.[24,25] The ACG recommends weight loss for patients who are overweight and those who have experienced recent weight gain.[4]

While the ACG guidelines do not recommend tobacco or alcohol cessation to improve GERD symptoms, a prospective population-based cohort study found that smoking cessation was associated with decreased severe reflux symptoms in normal-weight patients.[4,26] Interestingly, no significant change in reflux symptoms was found in overweight or obese patients who quit smoking.[26]

Head of bed elevation is another lifestyle modification with support from RCTs. A crossover study of 15 patients with GERD found elevating the head of the bed by 10 inches with a foam wedge decreased the esophageal acid exposure time compared to a flat position (15% vs 21%, respectively; $P < .05$).[27] However, there was no observed difference in reflux frequency among the positions in this study. A second study assessed the elevation of the head of the bed with 28 cm blocks and found a decrease in both the percentage of time the esophageal pH was below 5 and number of reflux episodes.[28] The ACG recommends head of bed elevation with a foam wedge or blocks in patients with nocturnal GERD.[4]

The data supporting dietary interventions are inconsistent.[23] Avoiding food intake near bedtime has been shown to be effective in reducing reflux frequency. An RCT comparing patients who ate 2 hours before bedtime versus 6 hours before bedtime showed more frequent reflux in those who ate the late evening meal.[29] Fiber also appears to help. A study by DiSilvestro et al found patients using a dietary fiber product for 2 weeks experienced an increase in the number of days without heartburn and decreased heartburn severity compared to those who did not use the fiber product.[30] The ACG recommends avoiding meals with high fat content within 2 to 3 hours of reclining, but has no recommendation regarding fiber intake.[4] The ACG does not routinely recommend avoidance of chocolate, caffeine, spicy foods, citrus, or carbonated beverages but supports selective elimination if a patient notes a correlation between the GERD symptoms and improvement with elimination.[4]

Discussion

While PPIs are among the most commonly prescribed drugs in the United States, it is estimated that between 25% and 70% of these prescriptions have no appropriate indication.[31] PPIs are initiated through various mechanisms. Many patients receive prescriptions for PPIs on physician diagnosis of GERD. Others initiate therapy either on their own or on recommendation from a pharmacist. Still others receive PPI therapy as stress ulcer prophylaxis during a hospital stay. While PPIs may be initiated in appropriate patients in each of the aforementioned examples, continued use may not be appropriate for all.

When PPIs are initiated in the primary care setting, the ACG recommends an 8-week course of therapy followed by an evaluation to determine whether continued therapy is necessary.[4] A study of one ambulatory practice found that PPI use was continued without documentation of reevaluation in 48.6% of paitents.[32] Self-care of GERD with PPIs should be limited to a 2-week course, but many patients continue therapy, despite resolution of symptoms. PPIs started for prophylaxis in the hospital should be discontinued on discharge. A study of hospital patients in Michigan found that while only 21.6% of patients took a PPI prior to admission, 42.7% of patients were discharged on PPI therapy.[33]

The risk for inappropriate PPI use is high. It is therefore important to consult patients regarding their use of PPIs and determine whether continued pharmacotherapy is necessary. Because of the nonprescription availability of PPIs, a through medication history, including over-the-counter product use, must take place. During this discussion, it is also important to make patients aware of the potential adverse effects of long-term PPI therapy to ensure the risks are weighed against the benefits of continued use. While there are certainly circumstances in which pharmacotherapy is not only appropriate, but essential (refractory GERD, erosive esophagitis, Barrett's esophagus), many patients may experience relief of GERD symptoms with lifestyle modifications and may be

more apt to try lifestyle modifications if made aware of the risks of long-term use of PPI medications.

The data implicating PPIs in the development of dementia and CKD are limited by the observational study designs and inconsistent results. There are still many unanswered questions regarding the risks of long-term PPI use, including the dose and duration of therapy at which these risks are heightened (if at all). Further interventional research is warranted in these areas. However, because of the established adverse effects and the potential for these emerging risks, a case should be made for the use of lifestyle medicine in the treatment of mild, uncomplicated GERD, especially in those patients who may be using PPI therapy inappropriately. Evidence supports weight loss, tobacco cessation (specifically in normal-weight patients), head of the bed elevation, avoidance of meals near bedtime, and increasing dietary fiber in managing GERD symptoms and esophageal acid exposure. AJLM

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