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Tracy Fehr

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Tracy L. Fehr

University of North Dakota

PERMISSION

Title: Prudent Use of Proton Pump Inhibitors in Gastroesophageal Reflux Disease: Implications for Primary Care Practitioners

Department: Nursing

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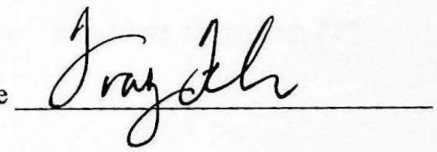
Signature 

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Abstract

Gastroesophageal Reflux Disease (GERD) is one of the most common conditions encountered in primary care. Proton pump inhibitors (PPIs) have become one of the most widely prescribed classes of drugs in both primary and specialty care for the management of GERD with an incredible one hundred and thirteen million prescriptions written by providers each year. PPI therapy has been proven to be effective in numerous randomized controlled trials to control symptoms associated with reflux disease and to normalize the impaired quality of life often reported by individuals with GERD. Proton pump inhibitors are the recommended course of treatment for uncomplicated GERD, and included in treatment guidelines created by the American College of Gastroenterology. Although PPIs are the preferred course of treatment for GERD due to their effectiveness and excellent safety profile, they can be associated with adverse effects and risks in certain patient populations. Therefore, PPI therapy should be guided by a careful risk/benefit analysis, coupled with patient education and follow up surveillance. This paper will present an actual case of GERD seen in a primary care setting, discuss the indications and implications for PPI therapy including the potential risks based upon a recent review of the literature, and finally, will make recommendations for primary care providers regarding PPI therapy using evidence-based management.

Background

Gastroesophageal reflux disease (GERD) is one of the most common conditions managed by primary care clinicians, and strategies to manage patients are applicable to both urban and rural practice settings. The prevalence of GERD is common and distributed equally among ethnic and cultural groups in the western world without regard to gender. Although GERD can occur at any age, disease incidence increases after the age of fifty. It has been estimated that as many as twenty-one to sixty percent of the U.S. population experience monthly heartburn symptoms, with up to ten percent of the adult population reporting daily symptoms. Occurrence is likely higher, as many individuals self-medicate with over-the-counter histamine blockers and/or antacids for symptom relief. Frequent heartburn sufferers will often attribute symptoms to stress or diet, and will not seek medical intervention until symptoms affect their quality of life. Gastroesophageal Reflux Disease becomes a clinical diagnosis when symptoms become more frequent and severe, and the potential for adverse clinical consequences become more probable (Katz, Gerson, and Vela, 2013).

Patients with GERD may present to their primary care provider complaining of a variety of symptoms ranging from persistent cough to chest pain, however, typical presenting symptoms are heartburn and regurgitation. Some symptoms have an established association with GERD including reflux cough, laryngitis, and asthma syndromes (Vakil, 2013). Using patient history alone, symptoms of heartburn and regurgitation are reliable in making a presumptive diagnosis, with a formal diagnosis dependent on response to antisecretory therapy (Katz et al., 2013). Atypical symptoms include epigastric pain, dyspepsia, nausea, bloating and belching and although indicative of GERD, may be associated with other conditions (Katz et al., 2013). Objective testing can be diagnostic using endoscopy and ambulatory reflux monitoring although

use of such testing is not warranted in cases which present with typical symptoms (Katz et al., 2013). Effective treatment of GERD is multi-faceted and includes a combination of life-style interventions and pharmaceutical management in tandem with diligent follow up and evaluation strategies.

The utilization of proton pump inhibitors (PPIs) as a therapy in the management of GERD is well established and based upon extensive clinical evidence. Guidelines established by the American College of Gastroenterology for the diagnosis and management of GERD include indications for use of PPI therapy, and include the identification of potential risks associated with PPI use. Some potential complications associated with PPI use include an increased risk of hip fracture and osteoporosis, an increased risk of community-acquired pneumonia, an increased risk of nosocomial Clostridium difficile infection and an increased risk for adverse cardiovascular events in patients concurrently taking clopidogrel (Katz et al., 2013). Evidence-based guidelines will be applied in the management of GERD as detailed in the case report to follow, and relevant recommendations for primary clinical practice will be identified based upon a comprehensive review of the literature.

Case Report

A sixty-five year old male presents to a primary care visit for evaluation of a recurrent, dry cough which has been present for approximately two months duration. He was initially evaluated and unsuccessfully treated with inhalers for a suspected bronchitis. His history reveals no recent upper respiratory symptoms or illness. The patient reports that the cough is worse at night, especially with recumbency, and is not relieved with cough drops or cough suppressants. He states the cough is non-productive, and is not precipitated by anything specific. His history reveals that he has taken lisinopril 20mg daily for hypertension for over a year, and the cough did

not correlate with the initiation of the lisinopril. He also reports frequent heartburn, and takes antacids on a daily basis with fair relief. He states that the cough and heartburn are affecting his ability to sleep, resulting in fatigue and increased stress.

The patient has no significant surgical or medical history, other than his hypertension. He is a former smoker who quit many years ago. He is married and works as a general contractor. He consumes alcohol occasionally, and does not use any illicit drugs. Family history is non-contributory to present illness. He is current on both influenza and pneumonia vaccines. He takes no medications other than lisinopril 20mg. daily and TUMS as needed for heartburn.

Review of systems reveals no recent change in weight or appetite. He denies fever, chills, night sweats and general malaise. He denies headache, lightheadedness and dizziness. He denies recent upper respiratory illness, congestion or rhinorrhea. He denies mouth and throat pain, lymph node/neck tenderness, and denies any difficulty swallowing.

Upon physical examination the patient is afebrile, with normal heart rate and respiratory rate but is slightly hypertensive at 149/88. He is pleasant, in no acute distress and is forthcoming during the interview and exam. His skin is warm, dry and intact. His neck is supple without palpable nodes and his thyroid is non-tender and non-enlarged. He has no JVD. S1 and S2 heart sounds are audible, no S3 or S4, murmurs, gallops or rubs appreciated. His respirations are even, regular and non-labored. Lungs are clear to auscultation throughout all lung fields without adventitious sounds or wheezing. He does exhibit an occasional, dry cough.

Diagnostic labs include a CBC and BMP which are both within normal limits. A CXR was not obtained based on his clinical presentation. Differential diagnoses included GERD, ACE-induced cough and allergies. ACE-induced cough was ruled out based on length of ACE

therapy, and allergies were ruled out based on review of symptoms and physical exam. He was diagnosed with suspected GERD based on history and clinical presentation.

Treatment strategies include lifestyle modifications to include avoidance of triggers such as acidic foods and caffeine, late evening meals and recumbent position after eating. He is also encouraged to elevate the head of his bed to decrease reflux. Pharmacologic treatment includes the initiation of esomeprazole 20mg. daily based on risk/benefit analysis. Patient education includes discussion of nature of the disease and indication for PPI therapy based on the clinical guidelines. He is instructed to follow up in the clinic in two to three weeks for evaluation of his GERD symptoms and re-evaluation of his blood pressure.

Review of Literature

Apart from the conventional lifestyle changes, it has become widely accepted that PPIs are the preferred medication for treating GERD using an eight week dosage-dependent course based on patient symptom severity. Proton pump inhibitors are more potent gastric acid secretion inhibitors when compared to histamine-2 receptor antagonists (H2RA), and effectively alleviate troublesome GERD symptoms while healing inflamed mucosa (Sheen and Triadafilopoulos, 2011). According to the latest guidelines established by American College of Gastroenterology, an eight week course of PPIs is the treatment of choice for symptom relief and healing of erosive esophagitis (Katz et al., 2013). Randomized, clinical trials have concluded that PPIs are more effective in controlling erosive reflux when compared to histamine blockers and placebo over a four to eight week period (Coca-Pelaz et al., 2013). Proton pump inhibitors have also been proven to provide faster, more complete symptom relief versus histamine blockers according to a review and consensus report using gastroesophageal reflux monitoring

(Sifrim, Castell, Dent and Kahrilas, 2004). Numerous PPIs are available both as over-the-counter preparations and prescription strength.

Currently, there are seven PPIs available, with three being available over the counter- omeprazole, omeprazole-sodium bicarbonate, and lansoprazole. The remaining four are available by prescription only- rabeprazole, esomeprazole, dexlansoprazole and pantoprazole. Studies have identified no major differences in the superiority of one PPI over another. A meta-analysis published by Gralnek, Dulai, Fennerty and Spiegel (2006), indicates no significant difference in relief of symptoms between agents. Switching from one PPI to another due to poor response is common in clinical practice, with limited data to support such action. However, data from one double-blind, randomized controlled trial by Fass, Sontag Traxler and Sostek (2006) demonstrates that in patients refractory to once daily lansoprazole, switching therapy to once daily esomeprazole was equally as effective as increasing the lansoprazole to twice daily dosing. According to the latest guidelines established by the American College of Gastroenterology, for patients with partial response to PPI therapy, increasing the dose to twice daily or switching to another PPI may provide improved symptom relief; however, there is no current data to support switching PPIs more than once in patients who do not respond adequately (Katz et al., 2013).

The above mentioned guidelines reported by Katz et al. (2013) note that approximately seventy to eighty percent of patients with esophageal reflux will demonstrate complete relief of symptoms after an eight week PPI trial. Current data recommend initiation of therapy with once daily dosing, preferably before the first meal of the day, with delayed release PPIs being the most effective in controlling gastric pH. However, many patients with GERD experience increased symptoms at night. In a randomized, four-way crossover study conducted by Lee, Mulford, Wu and Atkinson (2010), the PPIs most effective in gastric pH control independent of meal timing

were dexlansoprazole and omeprazole-sodium bicarbonate, which provided nocturnal symptom relief when dosed at bed time. A systematic review conducted by Pace, Tonini, Pallotta, Molteni and Porro (2007) demonstrates that in patients with non-erosive reflux disease (NERD) or uncomplicated GERD, most can be managed successfully with on-demand versus maintenance therapy. According to the American College of Gastroenterology guidelines , maintenance therapy beyond eight weeks is appropriate for patients who continue to have symptoms after the PPI has been discontinued, or in patients who experience complications such as erosive esophagitis and Barrett's esophagus (Katz et al., 2013). Additionally, step-down therapy to H2RAs in patients with NERD or mild GERD is an appropriate option if long-term maintenance is an issue, as control of reflux symptoms and progression of disease is the main goal of therapy, as supported by Pace et al., (2007). This does not include patients with erosive reflux disease, who often will require the most potent course of PPIs for management.

Proton pump inhibitors are generally well tolerated, however less than two percent of patients may report headache, diarrhea and dyspepsia (Katz et al., 2013). However, a potential for more serious adverse effects has been associated with PPI therapy. The effects addressed in this paper include potential for increased fracture risk, increased risk of community acquired infections and increased cardiovascular events in patients who also take clopidogrel. In fact, warnings have been issued by the FDA regarding the potential for fractures- specifically wrist, hip and spine, in addition to the potential for adverse cardiovascular events in patients taking clopidogrel. Multiple systemic reviews and meta-analyses have been conducted and published to investigate these potential adverse effects associated with PPIs.

According to Katz et al. (2013), by reducing gastric acid, PPIs have been proposed to inhibit osteoclast-mediated bone resorption. However, there have been varied results among

clinical studies to support or refute this proposal. In a systemic review and meta-analysis conducted by Ngamruengphong, Leontiadis, Radhi, Dentino and Nugent (2011), there is a modest association noted between PPI use and fractures, particularly of the hip and spine. However, the investigators note that the results should be interpreted cautiously, as the number-needed-to-harm is likely dependent on the baseline risk of patients in the study population. In two separate studies included in the meta-analysis, PPI therapy was not significantly associated with hip fractures in patients without other fracture risk factors (Ngamruengphong et al., 2011). Using this data, one can conclude that PPI use may only increase the risk of fracture among patients with other existing risk factors for fracture. Similar findings were found in a separate meta-analysis conducted by Eom et al. (2011b). This investigation identifies a link between PPI use and increased fracture risk especially in patients already at risk for fracture. The study further demonstrates that the risk for fracture is highest in patients on long-term PPI therapy, but interestingly, the authors found no significant association between increased fracture risk and long-term H2RA use (Eom et al., 2011b). This finding was reaffirmed in a study by Kwok, Yeong, and Loke (2010). This meta-analysis reports evidence to support the link between long-term PPI use and fracture risk, but found no elevated fracture risk in long-term use with histamine blockers. Therefore, it is reasonable to suggest that clinicians may wish to opt for H2RAs versus PPIs for patients at high fracture risk, especially when prescribing long-term therapy.

Risk of community acquired infection specifically pneumonia and enteric infection have been correlated with acid-suppressing drugs. An increase in gastric pH via acid suppression is thought to contribute not only to gastrointestinal infections, but respiratory infections as well. Findings from a meta-analysis conducted by Eom et al. (2011a), demonstrate evidence to suggest

a higher risk of both community and hospital-acquired pneumonia associated with the use of PPIs and H2RAs. Again, this study demonstrates that the highest potential risk exists for patients already at risk to develop pneumonia. Proton pump inhibitors were associated with a higher risk for community acquired pneumonia, whereas histamine blockers were associated with a higher risk for hospital-acquired pneumonia (Eom et al., 2011a).

Not surprisingly, a higher gastric pH encourages the growth of gut microflora. Gastric pH less than four has a bactericidal effect on host friendly organisms in the gut, and increased pH due to PPI use is thought to increase the proliferation of several bacterial pathogens whose spores survive in such environments (Bavishi and DuPont, 2011). One systematic review identified clostridium difficile (c-diff), Salmonella, Shigella and Camplyobacter as the primary organisms associated with PPI use and enteric infection (Bavishi and DuPont, 2011). PPI use and the link to c-diff infection is well studied and widely published, although there are conflicting results. Data from Bavishi and DuPont (2011) suggest two reasons for an increase in c-diff infections independent of PPI use: -an increased virulence in the strains, and an increase in host vulnerability. However, these variables when combined with altered gut flora (due to acid suppression) result in an increased risk for enteric infection. Based on the most recent and available evidence, the guidelines established by the American College of Gastroenterology recommend that PPIs be used judiciously in patients who are at risk for acquiring enteric infection including the elderly and those with co-morbid conditions (Katz et al., 2013).

Finally, a potential for undesirable interaction exists between PPIs and other drugs metabolized via the cytochrome P450 system. Once the PPI is absorbed, the cytochrome P450 system is primarily responsible for the drug's metabolism. According to Sheen and Triadafilopoulos (2011), some PPIs inhibit the components of this enzyme system, altering the

metabolism of other drugs. However, the above authors stress that such reactions are clinically uncommon and therefore, insignificant. In 2009, the FDA released a warning to providers regarding a potential for adverse cardiovascular events for patients using PPIs and clopidogrel therapy concurrently (Sheen and Triadafilopoulos, 2011). Since that time, data have been inconsistent. The current biological hypothesis states that PPIs and clopidogrel share the same metabolic pathway via activation of CYP 2C19. Therefore, the antiplatelet activity of clopidogrel is potentially decreased in the presence of PPIs, increasing the risk for cardiovascular events. However, a meta-analysis published by Kwok, Jeevanantham, Dawn and Loke (2012), reports no consistent evidence to support an increased cardiovascular risk among patients who use proton pump inhibitors and clopidogrel concurrently. Further meta-analyses conclude that based on current data, there is not sufficient evidence to support an adverse cardiovascular effect in patients using PPIs and clopidogrel, as reported in the Guidelines for the Management of Gastroesophageal Reflux Disease, (Katz et al., 2013). Therefore, based on a high level of evidence, there is no data to support altered PPI therapy in patients on concomitant clopidogrel therapy.

Learning Points

Gastroesophageal Reflux Disease is a common ailment seen in primary practice, and requires diligent management. Providers should first encourage lifestyle changes and non-pharmaceutical interventions prior to the initiation of PPI therapy in patients suspected to have GERD. Measures such as weight loss in overweight patients, avoidance of foods which can trigger reflux such as chocolate, caffeine, alcohol, acidic and spicy foods is a good place to start. Avoidance of meals two-three hours prior to bedtime and head of bed elevation can also help alleviate nocturnal GERD symptoms in some patients. In patients who continue to experience reflux

symptoms despite non-pharmaceutical interventions, clinicians should consider a PPI trial. However, for some patients, the risks associated with PPI therapy may outweigh the benefits. Patients who are elderly, chronically ill, malnourished, immunosuppressed or osteoporotic are at increased risk for adverse events associated with PPI therapy. Based on the available evidence, when treating GERD with PPIs, clinicians need to risk-stratify patients and determine appropriateness of therapy. In patients who are deemed appropriate for PPI therapy, some general guidelines for PPI management in primary care include:

- An eight week course of PPIs is the preferred therapy for reflux symptom relief and healing of erosive esophagitis.
- There are no major differences between the PPI agents in terms of efficacy, although newer PPIs offer more flexible dosing with regard to meal timing.
- Therapy should be initiated with once daily dosing, before the first meal of the day.
- Symptoms should be re-evaluated in 2-3 weeks- For patients with partial response to once daily therapy, consider twice daily dosing *or* switch to a different agent.
- Non-responders should be referred for further evaluation.
- Maintenance PPI therapy is appropriate for those patients who continue to have symptoms upon the discontinuation of PPIs, and for patients with erosive esophagitis or Barrett's esophagus.
- Long-term PPI therapy should be prescribed at the lowest possible effective dose, and may include on-demand therapy.
- H2RA therapy is appropriate as a long-term maintenance medication in patients without erosive disease for symptom relief following an eight week course of PPIs.
- PPIs are safe and appropriate for use in pregnant women if clinically indicated.

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