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Proton Pump Inhibitors: An Overview of their Risks and Adverse Effects

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Abstract

The purpose of this literature review is to examine the risks of using proton pump inhibitors (PPIs). For decades, providers have been prescribing PPIs under the impression that the risks were minimal, but research has shown that there are serious risks associated with their use. Some of the risks include: clostridium difficile (c. difficile), community acquired pneumonia (CAP), bone fractures, drug interactions, and dementia. The risks and their statistical significance, along with the socioeconomic impact associated with these adverse outcomes, are discussed. The prescribing trends of PPIs and histamine-2 receptor antagonists (H_2RA) along with alternative therapies to treat gastroesophageal reflux disease (GERD) are also investigated. A case study is presented describing a common presentation of GERD. The treatment plan is reflective of the evidence presented and shows how providers can implement the current research when providing care for patients suffering from GERD.

Proton Pump Inhibitors: An Overview of their Risks and Adverse Effects

GERD affects millions of people worldwide. In fact, GERD is the most common gastrointestinal-related condition that primary care providers encounter in the outpatient setting (Mody et al., 2013). Heartburn and indigestion often accompany GERD and cause discomfort for many patients. It is reported that GERD is associated with "substantial impairment of health-related quality of life, decreased productivity, and considerable social and economic burden" and that 10% of patients with GERD have attributed work absences to the condition (Mody et al., 2013, p. 161). PPIs are taken to relieve the symptoms of GERD, peptic ulcer disease, and to treat damage to the lower esophagus or vocal cords due to acid reflux (Linsky & Simon, 2013). They work by blocking the acid production from the parietal cells in the lining of the stomach. PPIs are long-lasting acid suppressors. There are other medications used to treat GERD, but PPIs are the most effective (Friedlander, Pallentino, Miller, & VanBeuge, 2010). They have been around since the late 1980s and are the most prescribed medication for the treatment of heartburn and acid related stomach problems (Benmassaoud, McDonald, & Lee, 2016). In 2009, there were more than 95 million prescriptions written for PPIs (Department of Health and Human Services, 2010) and they have been one of the ten most commonly prescribed drugs in the last five years (Linsky & Simon, 2013).

In the past, providers have been quick to prescribe PPIs to treat GERD because they are so effective and carry minimal risk, but research is now available that reveals these medications might not be as safe as we once believed them to be. Due to the high percentage of patients who

use PPIs, it is important that providers fully understand the risks associated with them and other treatment options available. The elderly population is particularly vulnerable to these adverse reactions due to co-morbidities and polypharmacy (Fisher & Fisher, 2017). This literature review will highlight the complications that can arise with the use of PPIs. Considerations for providers prescribing PPIs and alternative treatment options will be presented.

Case Report

An 88-year-old female presented to her primary care office with a dry cough. She explained that it began about three months ago and she noticed it mostly at night after lying down in bed. Associated with the cough was a burning sensation in her throat. She tried codeine cough syrup and throat lozenges which were not helpful. Two months prior to this visit she was treated for bronchitis with an inhaler, but did not see improvement in her symptoms. In conjunction with her cough, she noticed that she was experiencing heartburn more frequently over the last three months. She was using OTC antacids but they provided minimal relief. She denied any difficulty swallowing, chest pain, or shortness of breath. She denied fever, chills, nausea, vomiting, fatigue, or night sweats. She denied any known history of, or exposure to, TB or recent travel to foreign countries.

Her medication regimen included Lisinopril 10 mg daily for hypertension and antacids as needed for heartburn. She did not have any known drug or environmental allergies. Her past medical history was unremarkable except for hypertension. She had not had any type of surgery except for her screening colonoscopy. Her family medical history was unremarkable.

Her social history included twenty-pack years of smoking, she quit twenty years prior. Her diet included mainly red meat and potatoes for dinner and a pot of coffee a day. She

admitted she had a sweet tooth and enjoyed eating chocolate. She reported that she lived at home with her husband, they were retired with two grown children, 6 grandchildren, and had no pets.

Her review of systems was grossly negative except for the previously mentioned concerns. Her blood pressure was 130/80, pulse 76, respirations 16 breaths per minute, and temperature 97.8. During the exam, the patient was seated on the exam table, dressed appropriately, and alert and oriented to person, place, and time. Her lungs were clear to auscultation bilaterally. Her heart rate was regular without murmur, click, gallop, or rub. Her TMs were pearly gray and not bulging. Her throat was without erythema and tonsils were not enlarged. Her nasal mucosa was moist and septum was not deviated. She did not have lymphadenopathy or growing masses. Her skin was free of lesions or rashes.

The provider diagnosed the patient with GERD and discussed conservative ways to treat her symptoms such as diet modification, elevating the head of bed, avoiding eating an hour prior to bed, and limiting her caffeine intake. The patient was receptive to the education and will follow-up in one month if the conservative measures are not effective, at which point a H_2RA blocker will be initiated. Patient was pleased with this plan of care.

Literature Review

Clostridium Difficile

The Food and Drug Administration (FDA) has acknowledged that the use of PPIs creates an increased risk of developing c. difficile and released a safety announcement in 2012 stating, "patients should immediately contact their healthcare professional and seek care if they take PPIs and develop diarrhea that does not improve" (FDA, 2016a). PPIs now require a package insert stating that there is an increased risk of c. difficile. The research of Abramowitz et al. (2016) is

concurrent and shows that there is a statistically significant increased risk of enteric infections, specifically c. difficile, with the use of PPIs.

C. difficile is a gram-positive bacterial infection that causes antibiotic-associated colitis (Up-to-Date, 2016a). Not only is it difficult to treat but the diarrhea associated with the infection is odorous, unrelenting, and can cause significant abdominal pain. According to the Centers for Disease Control and Prevention (2015), in 2011 nearly 500,000 Americans were infected by c. difficile and 29,000 died within 30 days of the initial diagnosis. Clearly, c. difficile is an infection that can be lethal, and the risk factors associated with the infection need to be evaluated.

There is not definitive research as to how or why PPIs cause c. difficile. However, it is believed that the reason for the increased risk of infection with PPI usage is due to the gastric pH being altered, which may help facilitate the infection (Abramowitz et al., 2016). Fisher & Fisher (2017) point out that the development of an infection is multifactorial, and "any medication likely to modify this balance might be involved in occurrence of infections" (p.2). This might explain why elderly develop c. difficile more frequently, due to their co-morbidities and polypharmacy (Fisher & Fisher, 2017). The duration of treatment or the dose do not appear to be related to the risk of infection with c. difficile (Abramowitz et al., 2016). However, recurrent c. difficile infection has been associated with continuous PPI use in 40-60% of patient infected with c. difficile (Fisher & Fisher, 2017).

Possibly the biggest risk factor in developing c. difficile while taking a PPI is the use of an antibiotic. There is a two-fold increase observed in those taking a PPI and an antibiotic versus a PPI alone (Fisher & Fisher, 2017). Although antibiotic use is a known major risk factor for c. difficile, data indicates that antimicrobial exposure alone is not the only variable, comorbidities

and medications may substantially contribute (Fisher & Fisher, 2017). Again, indicating why elderly, who are more at risk for polypharmacy, are at increased risk for c. difficile infections when using PPIs.

Even though strong evidence is available that indicates there is an increased risk of c. difficile with PPI usage, the relationship remains controversial. A meta-analysis including 37 case-control studies and 14 cohort studies failed to prove a cause-effect relationship (Fisher & Fisher, 2017). Still, an expert panel of infectious disease specialists agree that using PPIs increases your risk for a c. difficile infection, therefore, clinicians must carefully consider prescribing PPIs and the indications for their use (Fisher & Fisher, 2017).

Community Acquired Pneumonia

CAP has been linked to the use of PPIs. Several meta-analysis studies, which included more than 6 million patients, conclude that there is an increased risk of CAP, and the risk is highest in the first seven days of treatment initiation (Benmassaoud, McDonald, & Lee, 2016; Fisher & Fisher, 2016; Abramowitz et al., 2016).

The reason for the increased risk is not completely understood but there are a few theories. The risk of developing CAP is greater at the start of PPI therapy. This could be caused by the sudden change in the gastric pH which could lead to bacterial overgrowth (Abromowitz et al., 2016). Another potential cause can be drawn from a study that reported the depletion of gut microbes reduces immune-mediated resilience to pneumococcal pneumonia in mice (Fisher & Fisher, 2016).

The significance of the relationship between PPI usage and CAP is relevant. The number needed to harm (NNH) refers to how many patients would need to receive an intervention to result in an adverse effect. Based on their reviews, Abramowitz et al. (2016) determined that the

NNH was 333, which is relatively high. However, applied to the population level and considering how many Americans use PPIs, the number of patients who develop CAP could be substantial. As stated earlier, there were an estimated 95 million prescriptions for PPIs in 2010. If we divide 95 million by the NNH of 333 we get 285,285. This means every year 285,285 patients could develop CAP from using PPIs. Considering that around 50,000 people die from pneumonia yearly, the association between PPIs and CAP cannot be ignored (CDC, 2016).

Bone Fractures

Bone fractures occur at an increased incidence with PPI usage and they carry an FDA warning regarding this. In a safety announcement from the FDA in 2010 they warned that long-term (greater than one year) and high dose PPI use increased the risk of fractures of the hip, wrist, and spine (FDA, 2016b). This is consistent with the research of Abramowitz et al. (2016) who demonstrated that the relationship between PPI usage and bone fractures is statistically significant, with spine and hip fractures being the most common.

Not only are hip fractures common, they create a huge economic burden and cause an increased mortality rate. Each year more than 310,000 Americans are hospitalized for hip fractures, costing approximately 10.3-15.2 million dollars (Up-to-Date, 2016d). Several meta-analysis studies have determined the 1-year mortality to be up to 37% (Up-to-Date, 2016d). The socioeconomic burden of hip fractures is a significant public health concern, therefore making it prudent that providers carefully consider the indications for prescribing a PPI, which is a known risk factor for a bone fracture.

Dementia

There is also an association between PPI use and dementia. Dementia is a huge socioeconomic factor. The estimated worldwide cost of dementia is $818 billion, and by 2018 it will be a trillion-dollar disease (Alzheimer's Disease International, 2015). We know that primary prevention is the best way to reduce the occurrence of disease, so this has prompted dementia and cognitive impairment related to PPI use to be investigated. In a large cohort study in Germany, with more than 70,000 participants age 75 and older, there was a significant increase in the risk for dementia with the use of PPIs (Gomm et al., 2016). Another study in Germany assessed the association between the use of PPIs and the risk of dementia in the elderly population, $\geq$ 75 years. This study also concluded that patients receiving PPI medication had a "significantly increased risk of any dementia and Alzheimer's disease compared with nonusers" (Haenisch et al., 2015, p. 419). Corsonello et al. (2014) had similar results when they studied eleven geriatric and internal medicine acute wards located throughout Italy. They found the use of PPIs was associated with "functional decline in older adults discharged from acute care hospitals" (Corsonello et al., 2014, p.1113).

The underlying mechanism of how PPIs could be causing dementia is unknown, but there are a few theories. The first is that some PPIs cross the blood-brain barrier making them able to directly affect the brain and interact with brain enzymes (Gomm et al., 2016). Another possible explanation is that PPI use causes a B_{12} deficiency which is known to affect cognition and promotes neurological damage (Gomm et al., 2016; Corsonello et al., 2014; Haenisch et al., 2015). Based on this evidence it is important that providers are mindful that dementia or cognitive impairment could result from the use of PPIs in their elderly patients and consider alternative treatments when possible.

Drug Interactions

Drug interactions are another potential complication from PPI usage. PPIs increase the gastric pH which, in turn, impairs the absorption of other drugs. Other drugs influenced by PPI use are thyroid hormone replacement drugs, chemotherapy drugs, antifungals and antiretroviral agents (Benmassaoud, McDonald, & Lee, 2016). Fisher and Fisher (2017) report that the increased pH from PPIs can affect the bioavailability of several drugs including iron salts, ampicillin, and ketoconazole.

The interaction between Clopidogrel and PPIs is perhaps the most highly debated drug-drug interaction. Due to several clinical and observational studies that suggested an increased risk of recurrent acute myocardial infarction, the FDA recommended that Clopidogrel and PPIs be restricted (Masclee, Sturkenboom, & Kuipers, 2014). These studies, however, have considerable confounding and once confounding has been accounted for the association between PPI use and Clopidogrel disappears, which suggests the relationship is due to residual confounding (Masclee, Sturkenboom, & Kuipers, 2014). Nonetheless, drug interaction must be carefully considered when prescribing PPIs.

Inappropriate Prescribing

Many of these adverse outcomes could be completely avoided if PPIs were prescribed correctly. It is estimated that 25%-70% are prescribed inappropriately (Boghossian et al., 2017; Haenisch et al., 2015). PPIs are labeled and intended to be used for no more than 14 days. However, many people use them inappropriately and take them long-term which increases their risk of drug interaction and adverse events (Boghossian et al., 2017).

Several strategies have been developed to minimize PPI use and avoid inappropriate prescribing. Deprescribing is a new concept that some providers are using. Providers either use a

step-down approach by tapering off the PPI and starting a H2 blocker, or they just have their patients stop their PPI abruptly (Bohossian et al., 2017). One study from Linsky, Hermos, Lawler, & Rudolph (2011) observed the discontinuation of PPIs in the long-term care population and concluded that PPI discontinuation "did not result in subsequent resumption and infrequently led to H_2RA initiation" (p. 1662). Deprescribing may be more beneficial in the elderly population because they are more prone to polypharmacy which can lead to more drug interactions (Linsky & Simon, 2013). There are a few studies that show deprescribing approaches to be successful, however, there are no guidelines or evidence to show the long-term benefits or harms of deprescribing (Bohassian et al., 2017). Continued research on the benefits of discontinuing PPI therapy would be helpful to determine which patients should be have their PPI therapy discontinued.

Another strategy to avoid inappropriate prescribing of PPIs that has been trialed involved a 20-minute educational session paired with a prompt in the EMR that cued the provider to reassess for the appropriateness of PPI treatment. It was determined that 49% of patients did not have a clear indication for a PPI prescription and their PPI usage was discontinued prior to hospital discharge (Benmassaoud, McDonald, & Lee, 2016). Similar results were encountered when patients were sent to a nurse-led dyspepsia clinic where the nursing team developed action plans with patients to stop unnecessary PPI use. By month three 64% of 157 patients had stopped their PPI and another 30% had reduced their dose (Benmassaoud, McDonald, & Lee, 2016). This is significant because it demonstrates successful discontinuation of PPI therapy.

Yet another example of inappropriate prescribing is when patients take PPIs on an as needed basis. This form of misuse is not as easily controlled due to PPIs being available over-the-counter (OTC). If a patient has heartburn or reflux that warrants the need for stronger

medication than an antacid, they may be inclined to take a PPI because it is the strongest medication. The problem with using a PPI this way is that PPIs do not inhibit maximal acid output until day five, so they are not as effective on an as needed basis (Up-to Date, 2016a). With 69-86% of PPIs sold in outpatient retail settings, this population could be more at risk than we appreciate (Department of Health and Human Services, 2010).

Conclusion

PPIs have been a valuable medication and are necessary for the treatment of various gastric conditions and diseases, but as reviewed, there are also complications that must be considered when prescribing. Linsky & Simon (2013) state that "all adverse drug events, even perceived to be relatively minor, need to be balanced with potential benefits" (p. 524). Consideration of patient beliefs and preferences along with communication between providers and patients is essential. We are in the age of polypharmacy, so it is imperative that providers evaluate for an evidenced-based indication for each medication to determine its' medical necessity to reduce the incidence of drug interactions and adverse outcomes. Evidence-based indications to prescribe a PPI are as follows: a patient who has failed twice daily H_2RA therapy, a patient with erosive esophagitis, Barrett's esophagus, a patient with severe GERD that impairs quality of life, or a patient with a duodenal ulcer (Up-to-Date, 2016c). There are no off-label indications reported in the literature.

Some recommendations when diagnosing GERD and prescribing PPIs include: 1) Non-pharmacologic interventions should be trialed before medication is prescribed. Avoiding dietary triggers including caffeine, alcohol, tobacco, spicy food, chocolate, carbonated beverages, and peppermint (Up-to-Date, 2016c). 2) Elevate the head of the bed in patients with nocturnal symptoms and avoid eating two to three hours prior to bedtime (Up-to-Date, 2016c). 3) Providers

should consider early pH testing to establish acid reflux as the culprit, and if PPIs are warranted providers should prescribe the lowest effective dose (Schnoll-Sussman & Katz (2017). 4) If PPIs aren't working, look for alternative diagnoses and discontinue the use of PPI therapy (Schnoll-Sussman & Katz (2017).

Follow-up and reassessment on patients with GERD is necessary. Linsky & Simon (2013) point out "simply because a patient has tolerated a therapy for a long duration does not mean that it remains an appropriate treatment" (p. 525) and discontinuation should be attempted yearly. As described previously, more research is needed about the discontinuation of PPIs and the long-term effects. However, based on the potential adverse reactions, discontinuing PPIs should be considered if there is not an evidence-based indication. Schnoll-Sussman & Katz (2013) state, "perhaps most important, remind patients that medical management of GERD is not a substitute for a healthy lifestyle…" (p. 6). The adverse effects are uncommon, but due to their extensive use in the general population, the elevated percentage of PPIs being inappropriately prescribed and misused, and the lack of monitoring and reassessment, continued research in well-controlled randomized trials is warranted to determine the safety of PPIs.

In conclusion, primary care providers are frequently responsible for helping patients manage GERD. PPIs have been the go-to treatment options for many years and have provided great relief, but the risks associated with the use of PPIs are becoming a significant public health concern. Providers should remember these key points with their GERD patients.

- Determine if GERD is the true problem.
- Start with dietary changes and lifestyle modification. If those don't work H_2RA blockers can be initiated.

- Carefully consider the patient's co-morbidities and medication regimen. This is especially important for the elderly population.
- If PPI therapy is indicated, use the lowest dose that provides relief.
- Reassess the need for PPI therapy and discontinue if possible.
- Educate patients about the potential adverse reactions.

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