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Proton Pump Inhibitors (PPIs): A Review of the Efficacy, Usage, and Current Literature Recommendations

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Abstract

- As Klepser, Collier, and Cochran (2013) noted, PPIs are a class of agents that reduce acid secretion by parietal cells in the stomach by irreversibly blocking H+/K+ adenosine triphosphate. They are commonly prescribed for many gastrointestinal (GI) conditions including gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), upper gastrointestinal bleeding, and *Helicobacter pylori* infections. They are frequently utilized in the primary care setting. The purpose of this study was to examine the efficacy, usage, and current literature on PPIs.
- There were several complications noted with PPI usage. Gomm et al. (2016) found that that use of PPI is associated with an increased risk of dementia and that avoiding PPIs may contribute to the prevention of dementia. Klepser et al. (2013) concluded that PPIs were associated with renal disease after controlling for confounding conditions. They noted patients who had renal disease were twice as likely to have used PPIs in the past. In yet another study, Lazarus et al. (2016) concluded that PPI use is an independent risk factor for CKD and AKI, while H_2 antagonist use is not. Shih et al. (2014) concluded PPI use was associated with an increased risk of myocardial infarction for both a 7- and 14-day window period. Finally, van der Hoorn et al. (2015) also determined that PPI use was associated with a substantially increased risk of requiring osteoporosis medication and fractures.
- Histamine-2-receptor antagonists (H2RAs) are often prescribed in place of PPIs. Sigterman et al. (2013) concluded that were superior to H2RAs in treating heartburn in patients both treated empirically and in patents with endoscopy-negative reflux disease (ENRD). PPIs were also noted to be more effective in patients requiring long-term treatment. H2RAs, however, were found to be superior to PPIs in speed of relief of symptoms and may be a better option for patients with only occasional symptoms.
- Rickenbacher et al. (2014) studied medical vs. surgical management of GERD. Their data showed a statistically significant pooled effect estimate in favor of fundoplication over medical management of GERD, although several patients complained of dysphagia after surgery. Nissen fundoplication has long been the surgical intervention of choice for GERD treatment. It has some drawbacks in that many patients complain of dysphagia and bloating post-surgery. Lal et al. (2017) compared laparoscopic Nissen fundoplication (LNF) to laparoscopic anterior partial fundoplication (LAPF) and found it to be just as effective as LNF for GERD treatment with less dysphagia.

Introduction

- The stomach is the primary location of digestion, which is achieved through the release of acids and enzymes. Acid is secreted by the parietal cells.
- Acid-peptic disease is attributed to an imbalance between aggressive factors like acid, pepsin, and *Helicobacter pylori* infection, and local mucosal defenses such as secretion of bicarbonate, mucus, and prostaglandins.
- In western countries, duodenal ulcers are the most common gastrointestinal complaint, whereas in eastern countries, gastric ulcers are more common.
- We can treat acid-peptic disease by either reducing the aggressive factors, which is the most common method, or we can bolster the mucosal defenses in the stomach and duodenum.
- GERD, peptic ulcers, duodenal ulcers, Zollinger-Ellison syndrome, gastritis, and *H. pylori* infections are all treated by lowering gastric acid secretion.
- Acid secretion is currently reduced by blocking the acid secretary effect of histamine.
- This is achieved using two common treatments, H_2-receptor agonists or irreversible H^+/K^+-ATPase inhibitors. The latter are commonly referred to as proton pump inhibitors, or PPIs.
- If left untreated, disorders causing elevated gastric acid secretion can have serious consequences. These include scar tissue formation leading to pyloric stenosis, bleeding from erosion of small blood vessels, evolution of a gastric ulcer to cancer, or perforation. Perforation occurs more commonly in duodenal ulcers and may lead to complications involving other organs. (Jain et al., 2007)

Statement of the Problem

Proton pump inhibitors are very commonly prescribed medications throughout family practice clinics. Many different PPIs are now available over-the-counter as well. There are many possible diagnoses that may warrant PPI treatment and many patients take these medications for extended periods without medical provider supervision. Recently, studies have concluded that PPIs may have greater risks for patients than originally thought. This has led to the exploration of other treatment plans for these common GI conditions and complaints. This research hopes to answer the following research questions and determine if PPIs are the safest and most efficacious treatment for common GI conditions such as GERD, both duodenal and pyloric ulcers, and *Helicobacter pylori* infections. More research is needed to understand the interaction between these conditions and the reason for increased symptoms across the population. There also may be alternative methods of treatment not yet investigated or fully understood.

Research Questions

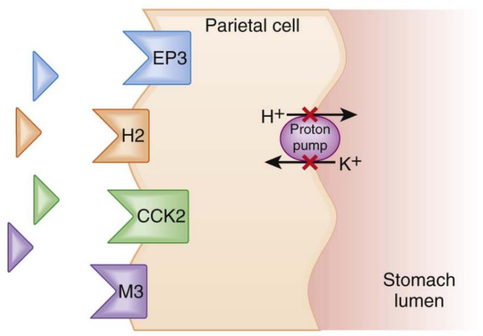
- In patients with GERD, duodenal and pyloric ulcers, or *Helicobacter pylori* infections, is treatment with PPIs more efficacious than treatment with histamine H2-receptor antagonists?
- In patients with GERD, duodenal and pyloric ulcers, or Helicobacter pylori infections, is treatment with PPIs more efficacious than surgical treatment?
- Does long-term treatment with PPIs increase a patient's risk for kidney failure, dementia, myocardial infarction, or osteoporosis?

Literature Review

Mechanism of Action of Proton Pump Inhibitors

- Gastric acid secretion is regulated by the proton pump in the parietal cell. The H^+/K^+-ATPase pump pushes H^+ into the stomach through an ion gradient.
- PPIs are absorbed into systemic circulation in the small intestine. They enter the parietal cells in the stomach from systemic circulation and are activated by the acid canaliculi.
- They irreversibly bind to the active proton pumps at the final step of acid secretion, reducing output.
- The basic chemical structure of a PPI consists of a substituted benzimidazole ring and a substituted pyridine ring connected to each other by a methylsulfinyl chain.
- The most commonly used PPIs include omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole.
- Research is currently being conducted on a new class of reversible PPIs, although none are available yet. (Jain et al., 2007)

Proton pump inhibitors (PPI)



Possible Complications of Proton Pump Inhibitor Use

- There may be drug interactions leading to decreased absorption of some drugs like griseofulvin, ketoconazole, vitamin B12, and iron salts. (Jain et al., 2007)
- Gomm et al. (2016) concluded that use of PPI is associated with an increased risk of dementia (HR 1.44; 95% CI 1.36-1.52; P<0.001) and that avoiding PPIs may contribute to the prevention of dementia.
- Klepser, Collier, and Cochran (2013) determined that PPIs were associated with renal disease after controlling for confounding conditions (OR 1.72; 95% CI 1.27-2.32; p<0.001). They removed patients with potential confounding disease states from the study population and were still able to statistically validate a relationship between PPIs and renal disease (OR 2.04; 95% CI 1.09-4.62). They noted patients who had renal disease were twice as likely to have used PPIs in the past.
- Lazarus et al.(2016) concluded that baseline PPI users were 1.72 times more likely to experience an acute kidney injury than those who did not use PPIs (95% CI 1.28-2.30; P<0.001). Twice daily dosing (adjusted HR 1.46; 95% CI 1.09-1.21; P<0.001) was also associated with a higher risk of CKD when compared to once daily dosing (adjusted HR 1.15; 95% CI 1.09-1.21; P<0.001). In this group, the 10-year absolute risk of CKD for the 16,900 baseline PPI users was 15.6% and the absolute risk for non-PPI users for CKD was 13.9%.
- Shih et al. (2014) found that PPI use was associated with an increased risk of MI for both a 7- (AOR 4.61; 95% CI 1.76-12.07; P=0.002) and 14-day window period (AOR 3.47, 95% CI 1.76-6.83, P<0.001).
- Van der Hoorn et al. (2015) determined that PPI use was associated with a substantially increased risk of requiring osteoporosis medication (adjusted sub-hazard ratio 1.28; 95% CI = 1.13-1.44) and fractures (adjusted sub-hazard ratio 1.29; 95% CI = 1.08-1.55).
- However, Katz, Gerson, and Vella (2013) concluded that five years of previous PPI usage did not increase risk of osteoporosis in the hip (OR 0.84; 95% CI, 0.55-1.34) or in the lumbar spine (OR 0.79; 95% CI, 0.59-1.06).
- Also, Targownik et al. (2016) found no difference between PPI users and non-users after DXA scanning (0.13±0.89 g/cm for PPI users vs. 0.12±1.07 g/cm2, P>0.2 for the non-PPI users). There was also no difference found in bone mineral density after CT scanning of the femoral neck. Metabolic markers were found to be statistically the same for both PPI users and non-users, except for gastrin, which was higher among PPI users, as expected.

Alternatives to Proton Pump Inhibitor Use

- Sigterman et al. (2013) concluded that PPIs (RR 0.37; two trials; 95% CI 0.32-0.44) were superior to H2RAs (RR 0.77; two trials; 95% CI 0.60-0.99) and prokinetics (RR 0.86; one trial, 95% CI 0.73-1.01) in placebo controlled trials treating GORD in patients empirically. In direct comparison, PPIs were more effective than H2RAs (RR 0.66; seven trials, 95% CI 0.60-0.73) and prokinetics (RR 0.53; two trials, 95% CI 0.32-.087).
- They also determined that in treating those with ENRD, the RR for heartburn remission for those treated with PPI vs. those treated with placebo was 0.71 (ten trials, 95% CI 0.65-0.78) and for H2RA vs placebo was 0.84 (two trials, 95% CI 0.74-0.95). The RR for PPI vs. H2RA was 0.78 (three trials, 95% CI 0.62-0.97) and for PPI vs. prokinetic it was 0.72 (one trial, 95% CI 0.56-0.92). H2RAs were noted to be effective, but to a lesser degree. (Sigterman et all., 2013)
- Rickenbacher et al. (2014) showed a statistically significant pooled effect estimate in favor of fundoplication over medical management of GERD (SMD 0.18; 95% CI 0.01-0.35).
- Lal et al. (2017) determined that laparoscopic anterior partial fundoplication is as effective as laparoscopic Nissen Fundoplication for GERD treatment.

Discussion

- Research continues of the possible consequences of PPI use and alternative treatments.
- Research revealed PPIs are more efficacious than treatment with histamine H2-receptor antagonists and prokinetics.
- H2RAs were suggested as an effective treatment option for those with occasional symptoms requiring intermittent treatment.
- When prescribing PPIs, providers must be aware of short vs. long-term course of treatment and plan accordingly while taking the patients overall health into consideration.
- In reviewing the literature, surgical treatment may be more efficacious than treatment with PPIs.
- After surgery, the amount of PPI dose required was generally found to be less than prior to surgery, which may help avoid some of the complications of long-term PPI use.
- Lal et al. (2017) lists surgery as the better option for long-term control of symptoms and for preventing new onset as well as regression of Barrett's metaplasia.
- In reviewing the research, there appears to be a strong correlation to long-term PPI use and kidney failure, dementia, and myocardial infarction.
- There is some argument to the belief that PPIs cause osteoporosis, although this is still being debated.

Applicability to Clinical Practice

- PPIs are one of the most commonly prescribed medications by primary care providers (PCPs).
- PPIs are available by prescription and over-the-counter.
- Specific populations may be at greater risk of harm from PPI use.
- Many factors should be weighted when determining treatment like severity of symptoms, patient life expectancy, quality of life, other chronic conditions, surgical candidacy, and adherence to treatment regimens.
- American Gastroenterological Association gives lifestyle changes a grade B recommendation. These include elevating the head of the bed and avoiding trigger foods. (Kahrilas et. al., 2008)
- Monitor those on PPIs for deterioration using recommended screening such as basic lab draws and DEXA scanning.
- PCPs should discuss complications and treatment options with patients to allow them to make an informed decision on their clinical course for common GI conditions like GERD, *H. pylori*, and duodenal and peptic ulcers.

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