Proton Pump Inhibitors (PPI)

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Abdelwahab Ahmed, John O. Clarke

Continuing Education Activity

Proton pump inhibitors represent a class of medications used to treat a wide variety of pathologies related to the stomach's acid production. This activity reviews the indications, action, contraindications for proton pump inhibitors as a valuable agent in managing acid-related disorders. This activity will highlight the mechanism of action, adverse event profile, and other key factors (e.g., off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions) pertinent for members of the interprofessional team in the treatment of acid-related disorders.

Objectives:

- Identify the mechanism of action of proton pump inhibitors.
- Describe the potential adverse effects of proton pump inhibitors.
- Review the appropriate monitoring for patients on proton pump inhibitors.
- Outline interprofessional team strategies for improving care coordination and communication to advance proton pump inhibitor outcomes.

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Indications

Proton-pump inhibitors (PPIs) represent a class of drugs most prominently known for their use in acid-related disorders. Omeprazole, a drug belonging to this class, is among the top 10 most prescribed drugs in the United States. PPIs are derivatives of the heterocyclic organic molecule benzimidazole. They are often the first-line agents amongst gastroenterologists for the following:

1. Esophagitis
2. Non-erosive reflux disease
3. Peptic ulcer disease
4. Prevention of nonsteroidal anti-inflammatory drug-induced ulcers
5. Zollinger-Ellison Syndrome

6. Part of the triple therapy regimen for *Helicobacter pylori* infections

The FDA has approved the following PPIs as of 2015:

1. Omeprazole
2. Esomeprazole
3. Lansoprazole
4. Dexlansoprazole
5. Pantoprazole
6. Rabeprazole

PPIs also have utility in treating pediatric diseases. Currently, these drugs are FDA approved to treat symptomatic GERD in the short term and for healing eosinophilic esophagitis in the pediatric population.

As for non-FDA-approved uses, PPIs have been used as an add-on therapy for patients on antiplatelet therapy before or after endoscopic procedures with a high risk of bleeding sequelae, functional dyspepsia, and eosinophilic esophagitis. Touched on above, PPIs may also be useful in conditions that may result in heavy NSAID use, such as acute coronary syndrome or chronic pain, as a preventative measure against NSAID-induced ulcers. Furthermore, new research is exploring the potential anti-tumor effects of PPIs in the treatment of melanomas, multiple myeloma, colorectal cancer, lymphomas, metastatic breast cancer, and other cancer pathologies.

Mechanism of Action

Ultimately, PPIs function to decrease acid secretion in the stomach. The proximal small bowel absorbs these drugs, and once in circulation, affect the parietal cells of the stomach. The parietal cells contain the H+/K+ ATPase enzyme, the proton pump, that PPIs block. This enzyme serves as the final step of acid secretion into the stomach. Interestingly, PPIs are prodrugs activated only after undergoing an acid-catalyzed cleavage in the acidic secretory canaliculi of the parietal cells. Hepatic P450 enzymes degrade PPIs. While there are slight variations in the exact P450 enzymes that are dominant in the degradation of the variety of PPIs, most dominantly degrade by the action of CYP2C19. Understanding the metabolism of PPIs allows us to understand why some PPIs work better for some individuals than others. For example, those of Asian ethnicity tend to have increased bioavailability of PPIs and thus should be managed initially with lower dosages. Furthermore, as we age, the bioavailability of PPIs increases, and thus dosages in the elderly should also be closely monitored and adjusted accordingly. While other drugs can reduce acid secretion in the stomach, PPIs represent the most potent drugs for acid reduction.

Administration

The formulations of PPIs are often specifically designed to prevent premature activation by gastric acid. The delivery methods include:

- Enteric-coated tablets
- Gelatin capsules
- Coated granules as a suspension
- In combination with bicarbonate to temporarily neutralize luminal gastric acid

For immediate acid suppression, there are intravenous formulations for lansoprazole, pantoprazole, and esomeprazole.

As proton pumps recycle periodically in the stomach, it may take a few days for PPIs to achieve a full effect - and of note, their duration of action is slower than some other medications that affect acid production, such as histamine-receptor blockers. These medications are best administered before food intake as proton pumps become activated during meals, and administration of PPIs prior to food intake will enhance the drug's efficacy. For this reason, most practitioners recommend that the patient take the PPI first thing in the morning when taken once daily. If twice-daily dosing is employed, then a second dose is usually added approximately 30 minutes before dinner. For some select patients with nighttime predominance of symptoms, the timing of once-daily administration may change to 30 minutes pre-dinner.

Adverse Effects

As the usage of PPIs continues to rise, it becomes extremely important to understand the extent of their adverse effects. As the use of these medications is common, potential adverse effects have received significant media attention; however, it is essential to note that most of these associations have as their basis on low-grade evidence and observational associations rather than clear causation. The following is a description of the variety of adverse effects described in the literature.

Hypomagnesemia

Albeit a rare side-effect, PPIs may lower magnesium to a level not easily replenished by supplementation and only corrected with removal of PPI. Hypomagnesemia is a serious complication that predisposes the patient to tetany, seizure, muscle weakness, delirium, and cardiac arrhythmias. It is not yet entirely clear what causes this adverse effect, but one hypothesis suggests that it may be due to decreased active intestinal absorption of magnesium by the transient receptor protein channels (TRPM 6/7) that are stimulated by extracellular protons.

Infection

While the acidic environment of the stomach serves as an environment in which proteins become activated to perform certain functions, so too does it serve as a chemical barrier against bacterial infection. PPIs have correlations with an increased amount of *Clostridium difficile* infections, other enteric foodborne infections, and potentially increased risk of community-acquired pneumonia. While it is still unclear as to the exact mechanism for this increased infection risk, one hypothesis proposed that the decreased acidic environment of the stomach leads to bacterial overgrowth and increased risk of bacterial aspiration.

Rebound Acid Secretion

PPIs can increase the levels of gastrin, which in turn leads to increased proliferation of ECL cells. ECL cells produce histamine, which under normal circumstances, stimulates parietal cells to activate their H+/K+ ATPase and produce acid into the stomach. Because PPIs act a step further than histamine, this side-effect does not negate the effect of PPIs. However, the problem lies in the discontinuation of PPIs after prolonged use, which has been shown in some cases to result in acid levels higher than before the initiation of PPIs. This effect has been referred to as rebound acid secretion.

Vitamin Deficiency

When vitamin B12 enters the stomach, it is bound to a protein molecule, R-factor. For vitamin B12 to release from R-factor, proteases need to be activated by an acidic environment. Once activated, the peptidases release R-factor from vitamin B12 so that it may bind another molecule, intrinsic factor, for absorption at the level of the terminal ileum. Disruption of the stomach's acidic environment by PPIs may lead to a vitamin B12 deficiency, although this appears to be clinically rare. Additionally, iron deficiency has also been reported with prolonged PPI use, although the exact mechanism remains elusive. There is also slight malabsorption of insoluble calcium separate from food, which many believe to be subclinical in most cases.

Other Potential Associations

Due to the frequency of PPI administration, numerous other potential associations have been reported and have received significant attention. Conflicting data have linked PPI use with osteoporosis and bone fracture; proposed mechanisms include calcium malabsorption, increased gastrin, decreased vitamin B12, and potential proton pumps in the bone. However, the data are not consistent, and while there may be an association, there is not a clearly established etiology at present. Likewise, isolated retrospective analyses have suggested a potential link between PPI use and dementia, kidney disease, and heart disease. However, these associations have not occurred to date in prospective studies, and there have been significant concerns raised with the retrospective analyses given potential confounding. Moreover, for dementia and heart disease, in particular, the findings, even in retrospective analyses, have been inconsistent. Following the initial development of PPIs, there was a concern for potential malignancy given prolonged gastrin

elevation; however, while this was present in animal models, it has not been demonstrated in human patients. Evidence shows that fundic gland polyps increase with prolonged PPI use; however, these do not appear to have a link with malignancy.

Contraindications

PPI contraindications include patients with known hypersensitivity to that class of drugs, and their use requires caution in patients with severe hepatic disease. As mentioned above, PPIs undergo metabolism by the cytochrome P450 system of the liver, mostly by CYP2C19; hence, any severe dysfunction in this metabolization serves as a relative contraindication. That said, clinically, clinicians often use PPIs in patients with severe liver disease with increased monitoring. PPIs can also alter the activity of specific cytochrome enzymes and delay the clearance of certain drugs such as phenytoin, warfarin, and diazepam. As such, the use of these drugs requires caution in those undergoing PPI therapy. Furthermore, the stomach's acidic environment is necessary for the effective absorption of ketoconazole, and it is advisable to use other antifungals in the setting of long-term PPI use. Conversely, the same acidic environment potentiates the absorption of digoxin, and thus this drug's use merits extreme caution due to the severity of its side-effect profile.

Monitoring

There is evidence supporting the monitoring of magnesium (especially in kidney transplant patients). Monitoring of vitamin B12 levels in patients on long-term PPIs is more controversial but reasonable to consider in select cases. Currently, there is limited evidence to support bone density scanning and/or calcium supplementation as an effective means of reducing osteoporosis.

Toxicity

PPIs can lead to adverse reactions such as headaches, dizziness, skin rash, abdominal pain, diarrhea, back pain, and upper respiratory infections. Currently, there is no FDA-approved antidote for overdose.

Enhancing Healthcare Team Outcomes

Many patients take PPIs, and it is crucial to recognize when the indication for use no longer exists or when they are not working effectively for a patient. For example, approximately 50% of patients taking PPIs for non-erosive GERD do not have their symptoms eradicated. In these cases, it becomes important to communicate to the patient that an increase in the PPI dosage may be a viable option. However, given the number of potential side-effects associated with long-term PPI, it is reasonable for clinicians to prescribe the lowest effective dose for the shortest period possible and maintain an adequate level of rapport with patients to adjust according to their needs.

This is why an interprofessional team approach to using PPIs is necessary. Clinicians prescribe the medications, but nursing staff should be able to answer any questions about the drug, including how to watch for potential adverse effects. Pharmacists will check for interactions and reinforce counseling points from the nurse. All team members need to contact the prescriber in the event of an adverse event or therapeutic insufficiency. This will result in optimal patient outcomes when using this drug class. [Level 5]

Review Questions

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