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Mini Review

Safety and Long Term Use of Proton Pump Inhibitors - Can Side Effects be Reduced?

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Abstract

The management of acid peptic disease was revolutionized by the introduction of proton pump inhibitors (PPIs) into clinical practice. PPIs are considered as the most effective agents available for reducing acid secretion. The overuse and misuse of PPIs are considered as concerning; few adverse events have been reported during short term use, however, long term PPI use is associated with increased risk of mortality of institutionalized older patients especially in patients over 65 years old. The major side effects have been discussed. For long term treatment of mild cases of chronic reflux of acidic gastric contents into the esophagus, H_2 blockers may be a better option in terms of safety while for more severe cases, PPIs may be used for treatment and then switched to H_2 blockers for prophylaxis in an attempt to minimize the side effects produced from long term use of PPIs.

Keywords: *Proton Pump Inhibitors (PPIs); Safety; Treatment; Prophylaxis*

Introduction

The management of acid peptic disease was revolutionized by the introduction of proton pump inhibitors (PPIs) into clinical practice [1]. PPIs are considered as the most effective agents available for reducing acid secretion. Since the late 1980s, these medications have been used to treat various acid related disorders like peptic ulcer disease, eradication of *H. pylori*, treatment and prevention of gastro-duodenal ulcers associated with NSAIDS, Zollinger-Ellison syndrome, and management of gastroesophageal reflux disease (GERD) [2]. In 1990, the US FDA approved omeprazole (Prilosec), the first proton pump inhibitor, for the short-term treatment of gastroesophageal reflux disease, active duodenal ulcer, severed erosive esophagitis, and pathologic hypersecretory conditions. At this stage, the PPIs are the highest third selling drug category in the USA as 113 million prescriptions annually with sales exceeding 14 billion US dollars [3]. Some consider PPIs as overprescribed and should be prescribed only when required as they have side effects as well especially when use on long term basis [4].

Adverse events

The overuse and misuse of PPIs are considered as concerning; few adverse events have been reported during short term use, however, long term PPI use is associated with increased risk of mortality of institutionalized older patients especially in patients over 65 years old [3].

The major associations reported in the literature are outlined below [1,3]:

1. *Clostridium difficile* infection
2. Dementia

3. Pneumonia
4. Kidney disease
5. Micronutrient deficiency
6. Decreasing bone mineral density
7. Cardiac events

Cardiac events

Cardiac events have been raised intermittently about the increased risk of certain conditions like myocardial infarction, cardiac failure, and sudden cardiac death although the US FDA has not concluded that such an association is likely [4].

In patients taking clopidogrel (Plavix), gastrointestinal bleeding may occur in patients with risk factors for such a condition. The risk factors include previous gastrointestinal bleeding, advanced age, concomitant use of warfarin (Coumadin), glucocorticoids, or NSAIDs, and *H. pylori* infection. Upon the recommendations of the American College of Cardiology and the American Heart Association, the use of gastroprotective agents in patients with unstable angina or non-ST segment elevation myocardial infarction who were taking aspirin and clopidogrel and who had a history of gastrointestinal ulceration. Since the issue of such recommendation in 2007, studies have shown that there is an increased risk of reinfarction in patients taking clopidogrel and a PPI other than pantoprazole. This may also increase the risk of hospitalization. As a result, both the American College of Cardiology and the American Heart Association recommend the use of drugs other than PPIs such as histamine H_2 antagonists (e.g. ranitidine, famotidine) for patients taking aspirin and clopidogrel who require gastroprotection [3].

Hip fracture

A retrospective study in the United Kingdom found that there is an association between the long term use of PPIs and hip fracture. There was a substantially higher incidence of hip fractures in patients older than 50 and who used PPIs for more than one year. As the duration of using PPIs increased, the probability of hip fracture also increased. A similar study stated that an increased fracture risk in patients using long term PPIs who had at least one other risk factor such as diabetes mellitus, chronic renal diseases, and glucocorticoid use was also observed. The FDA as a result revised the labelling of all PPIs to include the increased risk of fractures of the hips, wrists, and spine [3]. The main cause of these fractures is considered to be calcium malabsorption secondary to proton pump inhibitors induced acid suppression [4].

Micronutrients deficiency

Malabsorption of food bound minerals such as iron, calcium, and zinc has been noted in long- term use of PPIs but deficiencies have not been reported. A decreased absorption of oral cyanocobalamin may be the cause of the low levels of vitamin B12 in people with prolonged used of proton pump inhibitors [4]. In a study done on 209 patients PPIs with a follow-up for 12 months, there was a significant association between reduction in iron body stores and vitamin B12 levels with the use of PPIs for 12 months. Prolonged use of PPIs affects iron and vitamin B12 status, but hypoferremia and vitamin B12 deficiency at the end of the study was established in only 3.8% and 2.9% of the subjects, respectively, without significant differences between PPI users and non-users [5]. An increase in gastric pH is a normal physiologic change in the GIT of older persons and is exacerbated by long-term PPI use. It is not likely for people with normal iron stores to develop iron deficiency anemia solely from PPI use. However, patients with low baseline iron stores may be more susceptible to further iron depletion with concurrent PPI therapy [3].

In 2011, the US FDA issued a drug safety alert regarding the potential association between PPI use and hypomagnesemia. Chronic hypomagnesemia may increase the risk of cardiovascular disease, diabetes, and osteoporosis. The pathophysiology of such a condition is not known or well understood [1].

Kidney disease

Renal manifestations of long term use of PPIs can be seen in the form of interstitial nephritis. The patients usually have variable symptoms of weight loss, malaise, fever, nausea, polyuria, and polydipsia [4].

Dementia

Several studies have linked long term use of PPIs in elderly patients with increased risk of developing dementia [1].

Pneumonia

Acid suppression allows ingested pathogens to colonize the GIT and relocate to the respiratory tract. Recurrence of community acquired pneumonia is greatly increased with long term use of PPIs. Physicians should weigh the risks and benefits before starting a PPI in patients being treated with pneumonia [3].

Gastric acid rebound

Discontinuation of PPIs will lead to a high level of gastric hypersecretion (gastric acid rebound). This may pause a difficulty for patients who try to discontinue PPIs after a long term of use [3].

Stress ulcer prophylaxis

Many patients admitted to the ICH have risk factors with stress ulcers. If active bleeding from the ulcers take place, a higher mortality rate is expected. Significant risk factors associated with GIT bleeding include coagulopathy and mechanical ventilation exceeding 48 hours. Stress ulcer prophylaxis is recommended especially following mechanical ventilation longer than 48 hours and coagulopathy (e.g. platelet count less than 50 X 10^9 per L), partial thromboplastin time greater than 2 hours, and major burn injury (more than 30% of body weight) [3].

Effective options in stress ulcer prophylaxis include PPIs, H_2 antagonists, antacids, and sucralfate. No medication is superior to another. To minimize adverse outcomes, physicians should discontinue PPIs in patients when they are discharged from the ICU if there are no other indications for therapy [3].

Conclusion

Chronic reflux of acidic gastric contents into the esophagus produces a wide spectrum of clinical symptoms. These symptoms can be mild episodic symptoms like heartburn or more severe like regurgitation without macroscopic esophagitis and chronic inflammation and ulceration [6]. For treatment of mild cases, H_2 blockers may be a better option in terms of safety while for more severe cases, PPIs may be used for treatment and then switched to H_2 blockers for prophylaxis in an attempt to minimize the side effects produced from long term use of PPIs.

Bibliography

1. Jaynes M and Kumar AB. "The risks of long-term use of proton pump inhibitors: a critical review". *Therapeutic Advances in Drug Safety* 10 (2019): 1-13.

2. Eslami L and Nasseri-Moghaddam S. "Meta-analysis Does Long-term PPI use Increase the Risk of Gastric Premalignant Lesions?" *Archives of Iranian Medicine* 16.8 (2013): 449-458.

3. Ament PW., *et al*. "Reducing Adverse Events of Proton Pump Inhibitors". *Annals of Family Medicine* 86.1 (2012): 66-70.

4. Mittal SH and Govil T. "Potential Adverse Effects of Proton Pump Inhibitors Mimicking Other Conditions". *Astrocyte* 2.3 (2016): 133-135.

5. Qorraj-Bylyqi H., *et al*. "Proton Pump Inhibitors Intake and Iron and Vitamin B12 Status: A Prospective Comparative Study with a Follow up of 12 Months". *Journal of Medical Sciences* 6.3 (2018): 442-446.

6. Rickter JE., *et al*. "Lansoprazole Compared with Ranitidine for the Treatment of Nonerosive Gastroesophageal Reflux Disease". *Archives of Internal Medicine* 160 (2000): 1803-1809.

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