REVIEW ARTICLE

Proton pump inhibitors use; beware of side-effects

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Abstract

Proton pump inhibitors are most widely prescribed medicines all over the world. Since their introduction in pharmacy, life of millions of people has changed completely. Their ability to inhibit acid secretion in stomach has changed the natural history of many once-dreaded conditions like peptic ulcer and gastroesophageal reflux disease. Operation like gastrectomy and partial gastrectomy are carried out very rarely. These medicines are considered very cost-effective, have excellent safety profile, and provide prompt symptomatic relief. However, they are not without side effects, and several warnings have been issued by the Food and Drug Agency of the United States about the risk of hypomagnesaemia, possibility of increased fracture risk, and reduction in efficacy of clopidogrel by concomitant use of proton pump inhibitors. But despite all these warnings, their use is still on the rise. This Review was planned to highlight side effects and drug interactions so that a practising physician may keep the rare but potentially devastating effects in mind while prescribing the pumps.

Keywords: Proton Pump Inhibitor, Acid secretions, Histamine 2 receptor blockers, side-effects.

Introduction

Since the launching of first histamine 2 receptor blocker in 1976, treatment of peptic ulcer disease was changed forever. Cimetidine was soon to be followed by Ranitidine, introduced in 1981 to become bestseller in 1988. These potent antisecretory agents were soon to be replaced by another even more potent group of medicines called proton-pump inhibitors (PPIs). First of its kind was Omeprazole, launched with name of Losec in 1988, to become largest-selling pharmaceutical agent ever in 1996. Lansprazole was second to be marketed in 1991, Pantoprazole in 1994, Rabeprazole in 1999, Esomeprazole in 2001, and Dexlansprazole in 2009.

The uses of PPIs are still on the rise. In a London-based audit in 1997, only 8% of inpatients were receiving PPI therapy.[1] Vliel et al reported in 2008 that 43% of patients were taking PPIs during hospitalisation in pulmonary wards.[2] Sadaf Shafi et al in 2011 reported 51% of patients on PPIs without a definite indication.[3] Another Karachi-based study said 47.2% patients were prescribed PPIs on their discharge card.[4] In another study published in 2013, 79% patients were taking PPIs,[5] clearly indicating an upward trends for PPI prescription.

Pharmacology and Mechanism of Action

The mainstay of acid production in stomach is the secretion of hydrogen ions by parietal cells located in gastric mucosa. Each hydrogen ion is exchanged for one potassium ion by hydrogen/potassium (H+/K+) — adenosine triphosphatase (ATPase) pump. These H+/K+ ATPase pumps, often called proton pumps, are irreversibly inhibited by PPIs and this is the action which brings about the desired clinical effect of suppression of gastric acid secretion.

All PPIs are substituted derivatives of benzimidazole, which is pharmaceutically inactive compound with short half-life of (0.6 - 1.9 hours), needs acidic environment of the secretory canaliculus of the stimulated parietal cells, with a pH of approximately 1.0. The inactive benzimidazole is converted to a cationic tetracyclic sulphonamide compounds which binds covalently to cysteine residues on the alpha subunit of H+/K+ ATPase enzyme molecule, thereby inhibiting acid production.[6]

Although half-life is short, but because of covalent binding with H,K-ATPase, duration of action is longer than expected, therefore approximately 70% of pumps are inhibited because PPIs can inhibit only active pumps and not all pumps are active during 90 minutes of their half-life. Acid suppression is therefore achieved by subsequent PPI doses. It takes about 48 to 72 hours to attain a steady state.

The oral bioavailability of PPIs is high and ranges between 81% and 91% for different preparations. The degree of acid suppression does not correspond well with maximal plasma drug concentration (Cmax) but correlates well with area under the plasma concentration-time curve (AUC).[7]

Once-a-day dosing achieves about 66% suppression of

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maximal acid secretion, to increase it further either increase dose or increase the frequency of doses. In clinical practice the later strategy works better. If they are used twice daily there is more chance that active proton pumps would be exposed to medicines and better acid suppression would be achieved. A good day-time control of pH and symptoms is achieved if PPI is given before breakfast. However, for nocturnal control a PPI with longer elimination half-life like Tenatoprazole is superior to others in the class.[8]

To improve acid inhibition, PPIs should have a longer half-life, because if it clears slowly it will remain available for pump inhibition. To achieve the same effect all PPIs are marketed in delayed-release enteric-coated form so that they do not get activated by acid in the stomach but they dissolve in the intestine from where the drugs take a detour through general circulation and appear at the doorstep of H+/K+ ATPase pumps located on parietal cells of gastric mucosa.

PPIs are extensively and rapidly metabolised in the liver by CYP450 family of enzymes; namely CYP2C19 and CYP3A4. These enzymes are prevalent in different proportions in different races with different genetic background, and there is difference among PPIs to utilise these enzymes in different proportions for their metabolism. These two factors determine their tendency to interact with other medicines. Although there is significant theoretical risk for drug-drug interaction, fewer clinically significant interactions have been reported in literature.

Although PPIs have excellent safety profile as far as short-term use is concerned, but with time, ever-increasing prescriptions coupled with increasing duration of use is raising concerns about possible side effects and interference with various metabolic processes. We are going to discuss about the side effects and their mechanism and effect of co morbidities and drug-drug interaction.

Effects on Gastric Mucosa

Chronic acid suppression caused by PPIs results in high pH which stimulates G cells in gastric antrum, causing hypergastrinaemia and inducing hyperplasia of enterochromaffin like (ECL) cells.[9] There had been much concern about ECL cell hyperplasia resulting in carcinoid tumours, because ECL cell hyperplasia is considered precursor of carcinoid tumours. This fear was based on studies in female rats, but in humans no relationship was found between use of PPIs and carcinoid,[10] it has been reported, albeit in a small percentage among patients with chronic atrophic gastritis secondary to pernicious anaemia, and people with Zollinger Ellison syndrome in combination with multiple endocrine neoplasia type-I.

Parietal cell hyperplasia, glandular dilatation, and fundic gland polyps are a sequence of changes that are observed in patients on long-term PPI therapy.[11] These sporadic fundic gland polyps are distinct from familial adenomatous polyposis syndrome with a tendency to become malignant.[12] They are benign and regress completely once PPI therapy is discontinued.[13]

Rebound acidity is a common phenomenon after cessation of antisecretory therapy. When inhibition of proton pumps is no more after cessation of therapy;[14] high levels of gastrin, hyperplasia of parietal cells, over-stimulation of ECL cells happen under gastrin influence, releasing histamine. All these factors contribute to rebound acidity. Other mechanisms involving rebound acidity are conversion of new pumps from inactive to active form at the canalicular surface of parietal cells, and the dissociation of disulfide bond between PPI and cysteine.

Enteric Infections

Gastric acid is a natural host defence against gastrointestinal infections and studies have reported colonisation and bacterial overgrowth in gastrointestinal tract in patients on long-term PPI therapy.[15]

A positive association is found between PPI use and spontaneous bacterial peritonitis (SBP) in hospitalised patients with cirrhosis and ascites.[16,17] But study by Campbell et, al, did not find the association between use of PPIs and SBP.[18] Although the association is controversial, but physicians need to be careful while using PPIs in patients with cirrhosis and ascites.

Infection with clostridium difficile (C-difficile) is most common and results in diarrhoea associated with antibiotic use. C-difficile is gram-positive, anaerobic spore-forming bacillus exists as acid-resistant spores in environment. Gastric pH increases after PPI treatment and provides a comfortable environment for germination of C-difficile spores and can reach intestinal tract where normal flora is already disturbed by antibiotics treatment. There is much published data to prove positive association between use of PPIs and C-difficile-associated diarrhoea (CDAD) in patients who received antibiotics.[19] Although the association exists, but the risk is quite modest and outweighs the benefit of use of PPI.[20]

PPI and Increased Risk of Community Acquired Pneumonia (CAP)

In a population-based case-control study of 7642 cases

with first diagnosis of community-acquired pneumonia on discharge paper from hospital during 2000 through 2004, strong association was found between recent initiation (7 days) of PPIs and community-acquired pneumonia (CAP),[21] though risk decreased with long-term treatment, In another prospective population-based study comprising elderly patients, among all patients almost entire increased risk of recurrent CAP was among those with recent commencement of PPI therapy.[22] However, the reason behind development of pneumonia soon after the commencement of therapy is still not well understood.

Risk of Osteoporosis and Fractures

The association between increased risk of fracture and metabolic bone disease with use of PPIs is complex. In 2006 a UK-based study suggested that risk of hip fracture was significantly high among PPI user, and increases further with increased duration and doses.[23] A cohort in Boston, USA, showed association of long-term PPI use with modestly increased risk of non-spine fracture in elderly people with low calcium intake, although no such association was found with H2 receptor antagonist (H2RA).[24]

The data and evidence is not uniform, but there is general agreement on the positive association keeping other co-morbidities in mind. The possible mechanism is effect of high pH due to PPI use, which reduces absorption of calcium and vitamin B12, resulting in decreased bone mineral density.[25] Food and Drugs Agency (FDA) issued a safety announcement of a possible increased risk of fractures of the hip, wrist, and spine with the use of PPIs.[26] But why same observation was not seen in H2RA is probably because of more profound acid suppression by PPIs than H2RA.

PPI and Clopidogrel Interaction

Clopidogrel is an anti-platelet medicine widely used in acute coronary syndrome and to prevent stent thrombosis, especially in drug-eluting stents in ischaemic heart disease. Clopedogril is often used in combination with aspirin. Together they pose significant risk of gastrointestinal bleeding; An American College of Cardiology (ACC) task force on clinical expert consensus document recommended use of PPI with dual antiplatelet therapy.[27] However, this happy marriage did not last long and the issue of pharmacological interaction between these two medicines was raised on the basis that both medicines shared common metabolic pathway.

Clopidogrel is a prodrug which uses CYP 450 enzyme system (CYP2C19) for activation in the liver. PPIs use the same CYP2C19 enzyme to convert from active to inactive form. It means they both compete for the same enzyme, competitively inhibiting CYP2C19 which is responsible for the activation of Clopedogril, resulting in reduced platelet inhibition.[28] PPIs use two enzymes in the liver for metabolism, namely; CYP2C19 and CYP3A4. Different PPIs use them in different proportions; therefore their effect on Clopedogril metabolism is different. Omeprazole was the first PPI with whose interaction was noted. Soon included in this group were Esomeprazole, Lansprazole and Pantoprazole. Pantoprazole is the one which although interacts but appears to be least inhibitory.

Available data suggests that Omeprazole has most significant interaction with clopidogrel.[28] A comparative study of Omeprazole, Esomeprazole, Lansprazole, and Pantoprazole suggested that Omeprazole and Esomeprazole were irreversible (or quasi-irreversible) metabolism-dependent inhibitors of CYP2C19, but the rest were not.[29] Another study evaluated 6 PPIs and concluded that Omeprazole and Esomeprazole were clinically relevant inhibitors of CYP2C19, compared to Lansprazole, Dexlansprazole, Pantoprazole, and Rabeprazole.[30] Use of Clopidogrel with PPI was associated with increased risk of death or re-hospitalisation from acute coronary syndrome (ACS) compared with use of Clopidogrel without PPI.[31]

Residual platelet aggregation (RPA) is considered a risk for re-thrombosis in patients undergoing coronary stenting. It was found that peri-procedural co-administration of PPIs significantly decreases the effect of Clopidogrel by increasing the RPA. Concomitant use of Clopidogrel and PPIs in post-percutaneous coronary intervention patients was associated with higher risk of major cardiovascular event.[32] In a recent multicentre analysis, the PPI-Clopidogrel interaction showed slight increased risk of myocardial infarction or death in elderly patients, but a major clinical relevance was not observed.[33] The Food and Drug Administration (FDA) issued an alert stating that PPIs might interfere with the effectiveness of Clopidogrel and that clinicians should re-evaluate starting or continuing treatment with PPI in patients taking Clopidogrel.[34] Although prospective randomised studies are needed to provide a definite answer about Clopidogrel-PPI interaction but safe practice would be to use PPIs only when a valid indication is present especially in patients on Clopidogrel. Use less inhibitory Pantoprazole or Rabeprazole should a need arise. There should be at least six-hour gap between the two medicines. PPI should be given in morning and Clopidogrel mid-day so that because of short half-life of PPIs no active drug would be

available to compete for the enzyme.

Electrolyte Disturbances and PPI

Magnesium (Mg) is one of the most important intracellular cation and is involved in number of vital intracellular processes. Acutely low levels of magnesium may contribute to the generation of cardiac arrhythmias, can also induce bradycardia, hypotension, neuromuscular hyper-excitability, tetany and seizures. Chronic Mg depletion causes atherosclerosis, and hypocalcaemia by impairing parathyroid hormone secretion which ultimately results in mineral bone disease. Among patients admitted with acute coronary syndrome, non ST-elevation myocardial infarction (MI) and ST-elevation MI, there was statistically significant association between the PPI use, low Mg level and cardiovascular event like arrhythmias.[35] In obese adults with type 2 diabetes mellitus, low serum Mg is associated with premature ventricular complexes.[36]

FDA issued a warning that low Mg level can be associated with long-term use of PPIs.[37] Hypomagnesaemia may occur after three months of treatment, but the incidence increases after one year of treatment. There are several case reports published which implicated PPI use as a cause of hypomagnesaemia which resolved after withdrawal of PPIs.[38,39]

Conclusion

PPIs are very effective anti-secretory medicines with excellent safety profile. As a symptom reliever they are far superior to histamine 2-receptor blockers, and because of their quick action health professionals tend to use them on a priority basis on their patients to achieve good results and patient satisfaction. With increasing use, newer side effects are seen in clinical practice. Some of the risks are very potent, while some risks are modest. This review summarised history, pharmacology, mode of action, side effects and drug-drug interaction with the possible mechanisms. We believe that despite all concerns and supporting data about complications associated with their long-term use, PPIs are still a cost-effective medicine when used with valid clinical indication. Moreover, a constant review of dose and duration is essential to make sure of patient safety.

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