INDICATION ANDSAFETY PROFILE OF PROTON PUMP INHIBITORS: A REVIEW

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ABSTRACT

Proton pump inhibitors (PPIs) are widely prescribed classes of antisecretory drugs, used in the treatment of gastric-acid- related disorders such as peptic ulcer disease, erosive esophagitis and gastroesophageal reflux disease and so on.Due to their favorable safety profile, theyare often being over prescribed and used for inappropriate indications. PPIs are considered as a well tolerated class of drugs, but recent studies have raised concerns regarding the long term safety of proton pump inhibitors. Long term use may be associated with uncommon but serious adverse effects such as Clostridium difficleinfection, increased risk of bone fracture, vitamin B12 deficiency, community-acquired pneumonia, hypomagnesaemia, acute interstitial nephritis (AIN). The current review reveals theapproved indicationsand possible adverse reactionsof proton pump inhibitors.

Keywords: Proton pump inhibitors, anti-secretory medication, Indications, Adverse reactions

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INTRODUCTION

Proton pump inhibitors (PPI) are antisecretory medications that are effectively used in the treatment of various gastric-acid-related disorders.They were first introduced in 1988, since then they have become the most potent gastric acid suppressing drugs currently available for clinical use. Due to their favorable safety and efficacy, its use has increased over the years making them one of the commonly prescribed medications in the world. Omeprazole (Losec) was first of its kind to be launched into the pharmaceutical market in 1988, which was followed by Lansoprazole in 1991, Pantoprazole in 1994, Rabeprazole in 1999, Esomeprazole in 2001 and Dexlansoprazole in 2009. [1]

PHARMACODYNAMICS AND PHARMACOKINETICS

Proton pump inhibitors (PPI) are acid activated prodrugs that reduce the gastric acid production by irreversibly blocking the hydrogen-potassium adenosine triphosphate (H^+/K^+ ATPase) located in the gastric parietal cell. H^+/K^+ ATPase is also known as "proton pump", hence acquiring the name Proton pump inhibitors.[2] When compared to H_2 receptor antagonists (H_2RAs) , PPI are superior as they block the H^+/K^+ ATPase which is the final step in gastric acid secretion, resulting in intense and long-lasting gastric acid suppression.[3] The pharmacokinetic profile of PPI is given in table 1.[2]

TABLE 1 : Pharmacokinetic Properties

Parameter	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Esomeprazole
Protien Binding (%)	95	97	98	96.3	97
Bioavailability (%)	30-40	80-85	77	52	64-90
$t_{1/2}$ (hr)	0.5-1	1.6	1-1.9	1-2	1-1.5
T_{max} (hr)	0.5 – 3.5	1.7	2-3	2-5	1.5
V (L/kg)	0.13-0.35	0.4	0.15	-	0.22-0.26
CL (ml/min)	400-620	400-650	90-225	-	160-330
Liver Metabolism	CYP2C19	CYP2C19	CYP2C19, CYP3A4	CYP2C19	CYP2C19
Urinary Excretion (%)	77	14-23	71-80	90	80

INDICATIONS

PPI are currently the treatment choice in several clinical conditions such as gastric ulcer, duodenal ulcer, treatment and maintenance of gastroesophageal reflux disease, eradication of Helicobacter pylori infection , treatment and prophylaxis for the nonsteroidal anti-inflammatory drugs (NSAID) induced ulcers and for pathologic hypersecretory conditions such as Zollinger Ellison syndrome. Due to their favorable safety profile, a large number of patients are prescribed PPI for unnecessary conditions and those patients on treatment for appropriate conditions are receiving high doses or on longer duration of treatment than required.[4]

The US Food and Drug Administration (FDA) have approved Proton pump inhibitors for following indications:

- Treatment of gastroesophageal reflux disease
- Healing and maintenance treatment of erosive esophagitis
- Treatment of gastric ulcers and duodenal ulcers
- Treatment and prophylaxis of NSAID induced ulcers
- Eradication of Helicobacter pylori infection along with antibiotics
- Management of pathologic hypersecretory condition like Zollinger Ellison syndrome

ADVERSE REACTIONS

PPIs are generally considered as a well tolerated class of medications with relatively low incidence of short term side effects. Their short-term administration may cause mild disturbances such as headache, nausea, diarrhea, abdominal pain etc.However several concerns have been raised related to long term safety of proton pump inhibitors. Long-term use may be associated with some serious adverse effects such as the following:-[5]

- Increased risk of bone fracture
- Hypomagnesaemia
- Vitamin B_{12} deficiency
- Clostridium difficile infection
- Pneumonia
- Acute interstitial nephritis

Recent studies have revealed that there may be an association between PPI use and bone fracture. This may be due to PPI induced hypochlorhydria resulting in calcium malabsorption. A meta-analysis revealed that short-term and long-term(>1 year) use of PPI were associated with increased risk of hip fracture. The risk of spine fracture was found to be 58%, (RR. 1.58), the hip fracture 26%, (RR. 1.26) and fracture at any site 33%,(RR. 1.33).[6]

PPI induced hypomagnesaemia was first reported in 2006, since then several other cases have been published. [7] The Medicines and Healthcare products Regulatory Agency (MHRA) and the FDA have issued a warning regarding the risk of low magnesium levels in patients on long-term PPI therapy. A meta-analysis by Cheungpasitporn et al. found that there is significant association with an RR of 1.43 (95% CI 1.08-1.88) and the risk of

developing hypomagnesaemia are higher in PPI users than non-users.[8]

A case-control study carried out by Lam JR et al. suggested that chronic use of PPI was associated with vitamin B_{12} malabsorption. [9] However additional studies are needed to establish a link between PPI use and impaired vitamin B_{12}absorption.

Raised gastric pH may promote colonization of ingested microbes and this can lead to increased risk of infections. A systematic review and meta-analysis of 42 observational studies by Kwok et al. showed that PPI use can increase the incidence of Clostridium difficile infection compared to non-users (OR. 1.74) and are at a higher risk of developing a recurrent infection with an OR of 2.52. [10] Similarly, a meta-analysis by Eom CS et al. came to the conclusion that the overall risk of either community-acquired or hospital-acquired pneumonia is higher in patients on PPI therapy (OR. 1.27).[11]The first case of omeprazole-induced acute interstitial nephritis (AIN) was published in 1992.Subsequenty, various reports on the occurrence of AIN due to pantoprazole, lansoprazole, rabeprazole and esomeprazole were publishedin the following years. To evaluate the risk ofacute interstitial nephritis in PPI users, a nested case-control study was carried out and the study found that PPI use is associated with increased risk with an OR of 5.16.[12]

TABLE 2: Potential Risks Associated With Proton Pump Inhibitors

	Proposed Mechanism	Strength of evidence	Risk	Recommendations
Risk of bone Fracture	Malabsorption	Weak	RR 1.58 (1.38-1.82)	Monitor Bone mineral density.[6]
Hypomagnesemia	Inhibition of intestinal magnesium absorption through TRPM 6 & 7 channels	Unknown	RR 1.43 (1.08-1.88)	Monitor serum magnesium levels of patients on long-term PPI therapy.[8]
Vitamin B_{12} deficiency	Malabsorption	Weak	OR 1.65 (1.58-1.73)	Recommended routine screening in weak /elderly patients on long-term PPI therapy.[9]
Clostridium difficile Infection	Alkaline gastric pH prevents the inactivation of ingested bacteria	Moderate	OR 1.74 (1.47-2.85)	Cautious use of PPI in patients with high risk of developing CDI.[10]
Pneumonia	PPI- induced gastric acid suppression leads to overgrowth of ingested bacteria and increase the risk of bacterial aspiration into the airway	Weak	OR 1.27 (1.11-1.46)	No recommendations.[11]
Acute interstitial nephritis	Idiosyncratic reaction	Moderate	OR 5.16 (2.21–12.05)	Immediate discontinuation of PPI.[12]
PPI- Proton pump inhibitor, TRPM channel- Transient receptor potential melastatin channel, CDI- clostridium difficileinfection, CKD- Chronic kidney disease, RR- Relative Risk, OR- Odds Ratio				

CONCLUSION

PPI therapy plays an important role in the management of various clinical conditions such as gastric ulcers, duodenal ulcers,erosive esophagitis ,gastro esophageal reflux disease etc. However in majority of cases PPI are prescribed without a clear clinical indication. This can lead to increased financial burden and healthcare related consequences. Therefore, attention should be brought towards appropriate use of PPI so that patients can benefit from their treatment

without the fear of safety concerns associated with them. Thus we are able to achieve better patient care.

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