

Proton Pump Inhibitors (PPIs) are among the most prescribed medications. Millions of people are using it for two major indications viz. (1) Treatment of Dyspepsia, and (2) Prevention of Gastrointestinal (G.I.) Bleeding in patients prescribed Anti-Platelet Drugs (Aspirin ± Clopedogril), Anti-inflammatory Drugs, Stress situations (in ICU). PPIs are prescribed for a prolonged period of time, with a belief that they are safe and have fewer side effects. That is why they are over-prescribed, often unnecessarily for a prolonged period. Once prescribed, most Indian patients continue to take PPIs for years even after symptomatic relief and would not re-consult the Physician. Most of the evidences supporting the adverse effects are observational studies. It is possible that PPI users are sicker than non-users or the adverse effects are caused by other drugs or confounding conditions.

Multiple high quality observational studies, avoiding potential confounding factors have shown causal relationship of adverse effects with PPI use. PPIs have been associated with adverse effects on Kidney, cardiovascular system, Clostridium difficile infections, Hypo-magnesaemia and Calcium absorption. The possible potential mechanisms of AE of PPI's are listed in Table 1.

KIDNEY DISEASES

Use of PPIs is associated with an increased risk of acute kidney injury, possibly mediated through acute interstitial nephritis, which is 3 fold higher in PPI users compared with non-user. The risk of development of chronic kidney disease is 50% higher in PPI users. Patients taking twice daily PPIs are at higher risk compared to once daily PPI users. Longer the patient uses, higher is the risk. There is higher risk among PPI users compared to patients using histamine (H₂ Antagonists). Use of PPIs may lead to chronic kidney disease through recurrent acute kidney injury and hypomagnesemia. Any patient with unexplained serum creatinine rise or urine analysis abnormalities, PPI induced ATN should be considered, prompting nephrology consultation.

HYPOMAGNESEMIA

Meta-analysis of 9 observational studies including 109798 participants found that PPI users had a 40% higher risk of development of hypomagnesemia compared with non-users. This increased the risk of kidney disease and non-recovery of renal functions after acute kidney injury, if not corrected in time. The development of severe Hypomagnesemia can lead to muscle weakness, tetany,

convulsions, cardiac arrhythmias and hypotension, Magnesium supplementation alone may not correct low serum magnesium levels unless the PPI is discontinued.

US Food and Drug Administration (FDA) issued a warning in 2011 that use of PPIs may cause low serum magnesium levels if taken for prolonged period of time.

INFECTIONS

- A. Clostridium Difficile Infection: Proton pump inhibitors (PPIs) reduce gastric acidity which may promote bacterial colonization in gastro-intestinal tract increasing the risk of infection. A meta-analysis of 39 studies showed a 74% higher risk of developing C. difficile infection as well as 2.5-fold higher risk of recurrent C. difficile infection among PPI users compared with non-users. FDA published a safety alert in 2015, warning for association of PPIs and C. difficile infection.
- B. Pneumonia: Use of PPIs reduces gastric acidity and increases bacterial colonisation in stomach, which may also lead to increased rates of Pneumonia. A meta-analysis of 5 observational studies showed that risk of community acquired pneumonia was 34% higher among patients using PPIs compared with non-users. The risk was higher with increasing dose of PPIs. However, risk for hospital-acquired pneumonia was not increased. Contrary to this meta-analysis, a retrospective cohort study evaluated the risk for community acquired pneumonia among more than 4 million patients newly prescribed non-steroidal anti-inflammatory drugs.

In these patients, PPI therapy was started (presumably for prevention of dyspepsia, ulceration and bleeding), there was no increased risk of hospitalization for community-acquired pneumonia compared with non-users. The result of this study may be more reliable than other observational studies because study population did not have gastric or oesophageal disease. This study shows that the risk of pneumonia is probably not increased.

CARDIOVASCULAR EVENTS

Patients with coronary artery disease, who have undergone coronary stent placement, are generally prescribed anti-platelet therapy to reduce the risk of coronary events.

Proton Pump Inhibitors are often prescribed along with

Table 1: Possible Potential Adverse Effects (AE) of Proton Pump Inhibitors

Adverse Effect (<i>↑ed risk with PPI's compared to Non-users</i>)	Possible Mechanisms	Possible Measure to Prevent AE of PPI's
Bone Fractures Even after use of PPI for <1 yr	↓ed intestinal Ca absorption → ↓ed bone density & ↑ed risk of fractures <ul style="list-style-type: none"> • Hip fractures – 26%, • Spine fractures – 58% • Fracture any site – 33% 	Avoid prolonged PPI use
Clostridium difficile 74% higher risk & 2.5 fold higher risk of recurrence	PPI's reduce gastric acidity, promotes bacterial colonisation of C. difficile infection	FDA issued safety alert in 2015, warning of possible association of PPI's & C. difficile infection and advised to avoid prolonged use of PPI's
Community acquired Pneumonia 34% higher risk. No ↑ed risk of hospital acquired pneumonia. Contrary to this other large study did not show such high risk.	Reduced gastric acidity leads to ↑ed bacterial colonisation in stomach which may increase risk of pneumonia	Avoid prolonged use of PPI's
<ul style="list-style-type: none"> • Acute Interstitial Nephritis ↓ • Acute Kidney Disease ↓ • Chronic Kidney Disease 	<ul style="list-style-type: none"> – 3 fold higher – 2.5 fold higher – 50% higher risk 	<ul style="list-style-type: none"> • Avoid twice a day PPI & its prolonged use, • If possible replace PPI with H₂RA, when less severe symptoms • Any unexplained rise of serum creatinine/urine abnormality suspect for prolonged use of PPI
Such AE not seen with use of H ₂ RA		
Hypo-magnesaemia – 40% higher risk when PPI's are used for a prolonged time	Hypo-magnesaemia increases the risk of acute kidney disease & non-recovery of renal functions if it is not suspected & corrected in time	<ul style="list-style-type: none"> • Only replacement of Magnesium would not be effective unless the PPI is discontinued
Reduced activation of Clopidogrel leads to 30% ↑ed risk of Cardiovascular events (in observational studies but not in RCT)	Clopidogrel is metabolised to its active form by liver enzymes cytochrome P-450, which also metabolises PPI's. This competitive inhibition reduces Clopidogrel activity.	<ul style="list-style-type: none"> • No clear clinical evidence for such a ↓ed Clopidogrel activity • Used PPI in the morning and Clopidogrel in the evening before Dinner.
Myocardial Infarction in general population (<i>16% higher risk in PPI users</i>)	Possibly arterial endothelial dysfunction	Yet not established

anti-platelet therapy to prevent gastrointestinal bleeding. *Clopidogril* is commonly used anti-platelet agent, which is metabolized to its active form by liver enzymes that also metabolize PPIs, suggesting that competitive metabolism by PPIs might lead to reduced activation of Clopidogril and thereby reduced anti-platelet effects. Pharmacological studies demonstrated that adding PPI to Clopidogril reduced platelet inhibition. This finding led the “FDA” in 2009 to warn against combining Clopidogril and PPIs.

A meta-analysis of 31 observational studies found that patients using PPIs with Clopidogril have a 30% increased risk of cardiovascular events.

Contrary to this observation, none of the 4 randomized clinical trials found an increases risk of coronary events,

when both drugs are co-prescribed. It is difficult to resolve these conflicting findings. The observational studies are much larger than the randomised trials and provide “real world” experience.

However, the observation studies are prone to section bias, and confounding, which are minimized by randomization. In Summary, there is no clear evidence that PPIs increase risk of coronary events in patients on Clopidogril.

A practical solution to avoid this competitive inhibition of PPI and Clopidogril, is to use PPI in morning and Clopidogril in evening.

RISK OF MYOCARDIAL INFARCTION

In 2015, a study from USA, in general population using large data of mining study indicates that persons using PPI's appear to be associated with 16% higher risk of myocardial infarction as compared to persons using H₂-blockers.

PPI use is associated with 2.22 fold increased risk of cardiovascular mortality.

FRACTURES

PPIs reduces intestinal absorption of calcium, which may decrease bone density and increase risk of fractures. Many observational studies have shown an association between PPI use and increased risk of fractures. In 2010, FDA published a safety alert noting a possible increased risk of fractures among PPI users.

A meta-analysis published in 2015 wherein 18 observational studies which included more than 2.5 Lakhs patients with fractures found that PPIs compared with non-users; 26 % higher risk of hip fracture, a 58% higher risk of spine fractures and a 33% higher risk of fracture of any site, even after short term use of PPIs for less than 1 year.

PPI & RISK OF DEMENTIA

In 2016, a German study of more than 70 thousand patients have observed that older age women more than 80 years who were using PPI's for more than 5 years, 77.9% women had a significantly increased risk of incidental dementia compared with patients not receiving PPI's. The study suggests that the avoidance of PPI medications may prevent development of dementia in females. PPI should be used for short periods of time and if symptoms are less, either stop PPI or replace it with H₂RA.

CONCLUSION

Available evidences suggest that PPIs are not that safe as claimed earlier. PPI use is associated with acute and chronic kidney disease, which is aggravated by hypomagnesaemia caused by prolonged PPI use, *C. difficile* infection and osteoporotic fractures.

Physicians should take precautions in prescribing PPIs in high risk patients and serum creatinine, magnesium levels should be monitored in patients using high doses for a prolonged period. The benefits of PPI use compared to

its potential harms should be weighed before prescribing PPIs in a given patient. Avoid using PPIs in patients with less severe symptoms or the fear of recurrence of symptoms of dyspepsia or heartburn that has resolved.

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