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PPI: AN OVERVIEW OF ADVERSE EFFECTS

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ABSTRACT

The literature on the long-term negative effects of proton pump inhibitors (PPIs) is compiled in this review. PPIs are widely used in both inpatient and outpatient settings for a variety of reasons. Although PPIs are typically thought to be safe and well-tolerated, increased and sustained use has been linked to more serious adverse effects. According to three meta-analyses, short-term PPI use raised the incidence of pneumonia by 27–39%. PPI use appears to be dose-related and is linked to Clostridium difficile infection (CDI). There have also been reports of fractures and poor absorption of minerals, especially vitamin B12. Conflicting findings have been found in studies looking at the possible connection between PPIs and vitamin B12 insufficiency; hence, a prospective study is required to determine any causal influence. The impact of these negative consequences should not be undervalued, even though only a small number of people experience them. Due to the widespread usage of PPIs, many people may be impacted by even a rare side effect.

KEYWORDS: Proton pump inhibitors(PPIs), adverse effects, longterm use, Clostridium difficile infection, micronutrient deficiency, chronic kidney disease.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most commonly used drugs in both outpatient and inpatient healthcare settings across the globe. The US Food and Drug Administration has currently approved PPIs for the treatment of several gastrointestinal conditions, including nonulcer dyspepsia, gastroesophageal reflux disease, and symptomatic peptic ulcer disease,

as well as for preventing gastrointestinal bleeding in patients undergoing antiplatelet therapy.[1]

They irreversibly inhibit the enzyme H+/K+ adenosine triphosphatase (ATPase) in the parietal cells of the gastric mucosa, thus reducing acid secretion. While PPIs have a short half-life (1-2 hours), this irreversible inhibition provides a longer effect, as new proton pumps need to be synthesised before acid secretion is resumed.[2]

PPIs have long been used to treat acid-related gastrointestinal disorders like peptic ulcers and gastroesophageal reflux disease (GERD). Still, an increase in their use has been well documented in many countries over the past few decades. The degree and duration of gastric hypoacidity caused by repeated PPI dosage greatly exceed the effects of competitive histamine 2 receptor antagonists (H2RA), and a phylogenetically well-preserved biological function is almost eliminated.[3] It seems that most of the side effects of PPIs come from their main purpose, which is to lower stomach acid, which can then cause direct or indirect harm. Short-term effects of PPIs are well understood, but the long-term effects of strong acid suppression are still unclear. This is because most studies have not followed patients for enough years to detect diseases that take a long time to develop.[4] Examples of commonly prescribed PPIs include omeprazole, esomeprazole, dexlansoprazole, rabeprazole and pantoprazole.

Table 1: PPI types and doses[5]

Type	Standard Dose	Administration route
omeprazole	10,20,40mg 40mg	Oral intravenous
lansoprazole	15,30 mg	Oral
	20,40mg	Oral
pantoprazole	20,40mg	Intravenous
	40mg	Oral
rabeprazole	10,20mg	Oral
	10,20,40mg	Oral
esomeprazole	40mg	Intravenous

POTENTIAL SIDE EFFECTS OF PPIS

PPIs are generally well tolerated and have few side effects. Short-term use may cause minor issues, such as headaches, rashes, dizziness, and gastrointestinal symptoms, including diarrhea, constipation, flatulence, nausea, and stomach discomfort. When PPIs are used at permitted dosages for a short period of time—roughly two weeks—doctors are generally

unconcerned about major adverse effects. However, as the usage of these medications rises, reports of side effects are growing, especially with long-term use.[6]

There is growing evidence linking PPI usage to several unfavourable clinical outcomes. Kidney problems, vitamin B12 insufficiency, hypomagnesemia, fractures, dementia, and cardiovascular events are some of these. Additionally, it has been suggested that patients are more likely to suffer infectious effects, the most common of which are pneumonia and Clostridium difficile infection (CDI).[5]

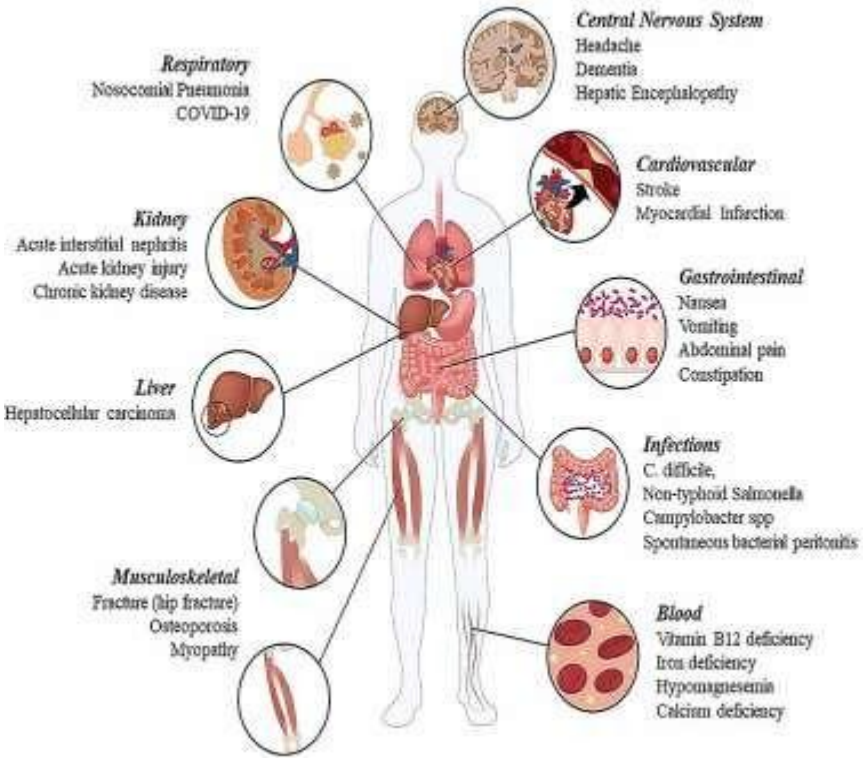

Figure 1: Side effects associated with the use of proton pump inhibitors.[7]

INFECTIONS

- **Clostridium difficile infection**

Research indicates that a high risk of Clostridium difficile infection is associated with low stomach acid levels. In the US, there are tens of thousands of cases each year, and over two-thirds of acid- suppressive medications given to patients are unnecessary.[8] When compared to H2RAs, PPIs show a significant association with higher susceptibility to CDI and recurrent CDI in children. The FDA has issued a warning regarding a potential connection between PPIs and Clostridium difficile infection, indicating that taking PPIs may increase the risk of developing diarrhea due to the presence of Clostridium difficile. Diarrhea that does not

improve in patients using PPIs should be assessed for Clostridium difficile-associated diarrhea (CDAD).[9]

- **Respiratory infections**

PPI use has been widely linked to pneumonia, particularly in the short term (typically less than 30-90 days). This link might be overstated, though, as a recent meta-analysis showed. PPI-induced hypochlorhydria promotes microaspiration of gastric contents, which increases lung colonization and the eventual incidence of pneumonia. This is the most plausible explanation for the increased risk of respiratory infections with PPI usage.(6,10) Furthermore, proton pumps have been found in the respiratory system, and the use of PPIs may change the respiratory tract's microbiota, potentially leading to pneumonia. While a recent randomized controlled trial (RCT) found no such association, meta-analyses of observational research have suggested that PPI medication raises the risk of pneumonia. Strict patient selection and limited statistical power may account for the RCT's null result, whereas confounding and selection may have influenced the relationships discovered in the meta-analyses.[11]

KIDNEY DISEASES

PPI use has been associated with acute kidney injury in case reports since 1992. More recently, two studies linked PPI use to an excessive risk of chronic kidney disease (CKD), which was not completely explained by the risk of acute kidney injury, with evidence that patients who used PPIs for longer periods of time had a higher risk of CKD.[4] Patients with documented diagnoses of CKD appear to progress quickly on PPI medication. The primary mechanism contributing to renal disease caused by PPI use could be acute interstitial nephritis. More than half of the patients who developed PPI-induced acute interstitial nephritis did not fully recover, implying that PPI-induced CKD results from the transition of acute interstitial nephritis with inflammatory interstitial infiltrates and edema to chronic interstitial scarring and tubular atrophy. Taken together, these findings provide strong evidence that PPIs cause acute interstitial nephritis and some evidence that they raise the risk of CKD.[12] Initially, physicians considered PPIs to inhibit other than gastric proton pumps, such as those in the renal tubule. However, definitive evidence of this in a clinical situation is missing.[7,12,14]

FRACTURE RISK

The increased risk of fractures caused by PPI use is a contentious issue. Retrospective studies have found a dose-dependent association between PPIs and decreased bone mineral density,

which leads to an increase in fracture risk, particularly hip fractures. Patients having a risk factor for osteoporosis, such as renal impairment, appear to have an increased risk. PPI users should have osteoporosis prophylaxis on a regular basis to avoid osteoporotic fractures.[7,15] Yet, more recent prospective studies revealed no appreciable short- to medium-term changes in PPI users' bone mineral density or fracture risk.[16,17] Long-term PPI-based therapy has been linked to reduced bone mineral density through a number of mechanisms, including gastrin-induced parathyroid hyperplasia, inhibition of bone resorption by blocking local H+/K+ ATPase, and hypochlorhydria-associated malabsorption of calcium (absorption of which is essential to maintaining bone microstructure).[7] Additionally, it was discovered that older women who used PPIs were more likely to experience recurrent falls.[18]

DEMENTIA

In general, there is inconsistent evidence about the relationship between PPI use and dementia risk. There is still disagreement among doctors regarding the function of PPIs and the dementia risk they pose. The majority of cases of brain dysfunction among PPI users have been linked to long-term PPI use, although the exact mechanism is unknown. Headaches and dizziness/vertigo are among the neurological side effects of various PPIs, including lansoprazole, esomeprazole, and pantoprazole. Depression, diplopia, disrupted sleep, sleepiness, insomnia, anxiety, tremor, sensory and perceptual abnormalities (such as hallucinations), and delirium are among the less frequently reported side effects involving the central nervous system.[19] The neurological effects of PPIs seem to be explained by their action on ionic pumps that regulate the membrane potential in neurons, albeit the exact processes are yet unknown. Individuals on PPIs appear to have less acidic lysosomes than individuals not taking them, which may reduce the ability of cells to break down amyloid-beta protein, the main material that builds up in the brains of Alzheimer's patients. Other theories include the indirect effects of PPI and H2 receptor antagonist use on systemic abnormalities (such as deficiencies in magnesium and vitamin B12).[20]

According to the 2015 World Alzheimer Report, dementia impacted about 46 million people worldwide as of that year. By 2050, this number is expected to increase to 131.5 million. The World Health Organization has prioritized dementia as a healthcare concern because of its detrimental effects on the economy and society, and the increasing number of dementia patients presents a substantial burden for healthcare systems. PPIs have been linked to an increased risk of dementia and Alzheimer's disease in older people in several studies. Comprehensive

research found a favorable relationship between PPI use and cognitive impairment.[9]

LIVER DISEASE

PPI use has been associated with a higher incidence of complications from cirrhosis, including liver cancer, spontaneous bacterial peritonitis, and hepatic encephalopathy. Patients who had more than a year of follow-up after starting PPI treatment had twice the risk of hepatocellular carcinoma compared to those who had less than a year of follow-up, suggesting that these outcomes are associated with long-term PPI usage.[21] Patients with liver disease may face a higher risk of liver damage due to medications. This is because PPIs, which can increase gastrin levels, are processed in the liver. The investigators also noted that cultured human liver cells exhibited gene expression patterns similar to those of known liver carcinogens after exposure to PPIs.[22,23]

GASTRIC NEOPLASIA

Long-term gastric acid suppression reduces intragastric acidity, causing compensatory hypergastrinemia due to loss of negative feedback on gastrin-secreting G cells. Gastrin acts as a powerful trophic hormone on enterochromaffin-like (ECL) cells by activating the CCK2 receptor, thereby increasing cell division, expansion, and abnormality. Sustained ECL cell stimulation over time leads to neuroendocrine tumour formation and may accelerate progression to gastric carcinoma, particularly in the gastric corpus and fundus. Gastric atrophy, chronic inflammation, and Helicobacter pylori infection all contribute to a benign state conducive to cancer. Experimental and clinical evidence of tumour regression following acid suppression or gastrin signalling blockade highlights hypergastrinemia's role in gastric carcinogenesis.[4,24]

CARDIOVASCULAR DISEASE

PPI use has been linked to cardiovascular morbidity and mortality throughout the past decade.[25] Long-term or high-dose PPI medication has been linked to an increased risk of significant acute cardiovascular events, such as acute myocardial infarction and stroke.[26] PPI use may lower endothelial nitrous oxide levels by inhibiting the enzymatic activity of dimethylarginine dimethylaminohydrolase, which clears asymmetric dimethylarginine and lowers nitrous oxide synthase activity. Chromogranin A, a crucial indicator of neuroendocrine tumors and a potential biomarker of cardiovascular disease, appears to be elevated in the blood by PPIs.[27,28]

MICRONUTRIENT DEFICIENCY

Gastric acid affects the absorption of minerals consumed as salts and protein-bound vitamin B12, according to numerous studies.[4]

- **Vitamin B12 Deficiency**

In order for B12 to bind to R proteins, it must first be released from food protein, which is made possible by gastric acid. The duodenum breaks down this B12–R protein complex, and once bound to intrinsic factor, B12 can be absorbed in the terminal ileum. Given that stomach acid is necessary for B12 absorption, long-term PPI use may theoretically reduce an individual's capacity for absorption. Conflicting findings have been found in studies looking at the possible connection between PPIs and B12; hence, a prospective study is required to determine any causal influence.[29] Furthermore, oral B12 supplement absorption should be unaffected because hypochlorhydria would only hinder the release of B12 from dietary protein. Studies on the potential association between PPIs and B12 have revealed mixed results, and a prospective study is needed to infer any causal influence.[29]

- **Calcium**

Calcium absorption may be hampered by profound acid inhibition.[30] Long-term PPI, on the other hand, does not appear to limit absorption of water-soluble calcium salts or calcium absorption from food, undermining the idea of altered calcium metabolism as a mechanism contributing to increased fracture risk.[31]

- **Iron**

Patients with stomach hypoacidity may not absorb iron as effectively, especially those who take medications like omeprazole and oral ferrous sulfate supplements. Interestingly, using PPIs seems to reduce the need for phlebotomy, while individuals with hereditary hemochromatosis absorb less dietary non-heme iron. Patients with hypoacidity caused by chronic atrophic gastritis also tend to absorb less iron. A large case-control study found that PPI use was associated with a higher risk of iron deficiency. However, for most people, the decrease in iron absorption is probably minimal, and its impact on health is still a topic of discussion.[32,34]

- **Magnesium**

Since 2006, there have been reports of hypomagnesemia among users of proton pump inhibitors (PPIs).[35] Numerous studies have indicated that individuals who use PPIs may have

an elevated risk of developing this condition. Although the variability among studies has made it challenging to conduct meta-analyses, a recent analysis found that PPI users have a higher risk of hypomagnesemia (relative risk [RR] 1.44) compared to non-users. Additionally, an examination of only high-quality studies revealed an even higher risk (RR 1.63). It appears that those currently using diuretics are at the greatest risk for hypomagnesemia, although this occurrence is relatively uncommon. While the exact cause of hypomagnesemia in PPI users remains uncertain, detailed analyses of case studies suggest that decreased intestinal absorption plays a significant role, rather than renal tubular loss. In conclusion, there is evidence of symptomatic hypomagnesemia in PPI users, but it is considered uncommon.[4,36,39]

CONCLUSION

When administered for brief periods of time, proton pump inhibitors have a favorable safety profile and are essential in the treatment of gastrointestinal problems associated with acid. However, data gathered in recent years indicates that long-term, careless PPI usage may be linked to a number of unfavorable clinical consequences. Long-term PPI therapy may be associated with infectious problems, renal impairment, nutritional deficiencies, neurocognitive consequences, hepatic dysfunction, gastric neoplasia, and cardiovascular events, according to findings from mechanistic analysis and epidemiological research. The long-term inhibition of stomach acid production and the ensuing physiological changes, such as hypergastrinemia and decreased nutritional absorption, are primarily responsible for these results.

Due to confounding factors and a lack of long-term randomized studies, the exact causality of many negative impacts remains unclear, despite some confirmed relationships in observational data. Infrequent side effects from proton pump inhibitors (PPIs) can pose significant clinical and public health concerns, given their widespread use. Thus, PPIs should be prescribed for specific indications, with personalized risk assessments and regular evaluations of their continued necessity. It’s essential to use the lowest effective dosage, determine the appropriate treatment duration, and consider deprescribing when possible. More extensive, long-term studies are needed to better understand risk profiles and guide safer prescribing practices.

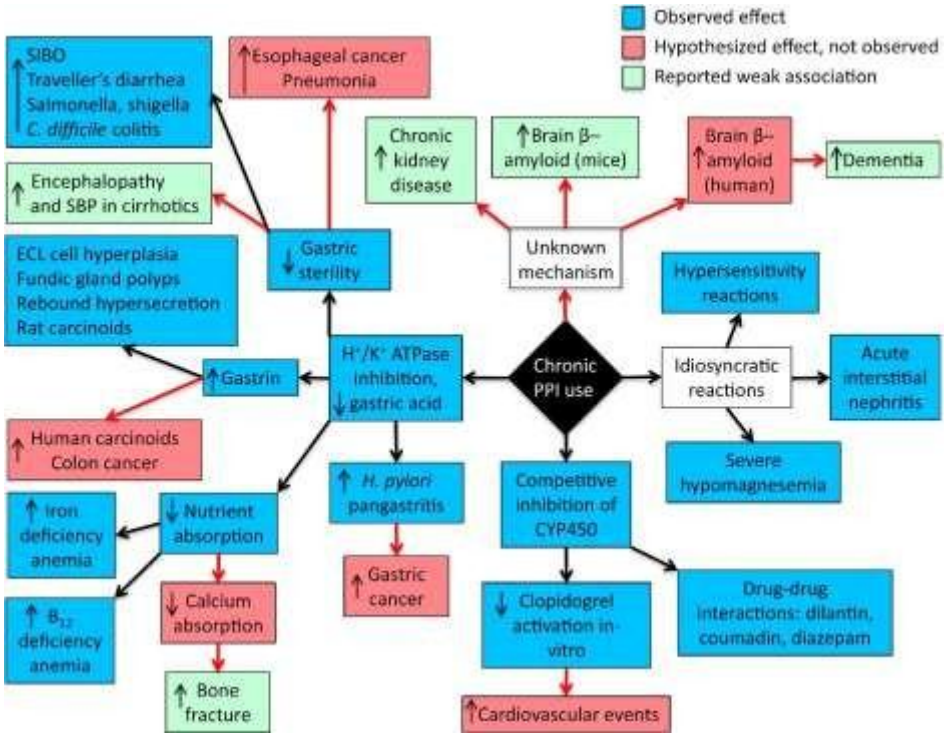

Figure2: Mechanisms of potential risks associated with PPIs.[40]

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