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A REVIEW ON PROTON PUMP INHIBITORS INDUCED DISEASES

Y. Narasimaha Rao*, Sirisha Chinta, K. J. S. V. Sireesha, Vinitha Sakhamuri, Sravanthi Vittala, Lavanya Thota

India.

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***Corresponding Author**
Y. Narasimaha Rao
India.

ABSTRACT

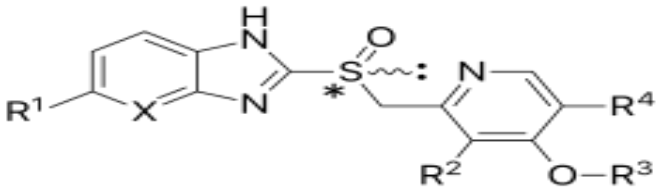
The proton pump inhibitors are most effective and mostly prescribed drugs in the clinics now-a-days and also used during multi drug therapy. They have a greater degree and longer duration action when compared to H2-receptor antagonist. Most commonly used drugs in PPI's are pantoprazole and rabeprazole. Due to the increased prescription of these drugs for longer durations can alter the health related life of the individuals. Long term use of these drugs may cause some disorders like PPI induced effect on mineral absorption& iron absorption, PPI induced enteric infections, PPI induced osteoarthritis, Dementia. So there is a major scope in knowing the long term effects of Ppi's.

KEYWORDS: Health related life, long term effects, and Proton pump inhibitors.

INTRODUCTION

The proton pump inhibitors are most effective and mostly prescribed drugs for symptomatic relief of gastric-acid related disorders and healing of gastric lesions. These are used extensively for the treatment of gastric acid disorders because they produce greater degree and longer duration of action when compared to H2 –receptor antagonist. As per current scenario ,most of the physicians are prescribing PPI's for treating gastric acid related disorders and used during multi drug therapy in order to reduce gastric irritation. PPI's are liable and tablets should be swallowed unbroken or uncrushed or they should be taken in the form of enteric coated granules, so this might be one of the reason for side effects of the drugs.

Structure



General structure of proton pump inhibitors

Drugs involved in PPI's

- Omeprazole
- Pantoprazole
- Esmoprazole
- Lansoprazole
- Rabeprazole
- Dexlansoprazole

Mechanism of PPI'S

These drugs inhibit basal and stimulated gasmine H2 receptor antagonists. Consequently, gastric acid secretion by inhibiting the H +/K+-adenosine triphosphatase (ATPase), also known as proton pump, that is located in the highly acidic domain of the parietal cell. Under acidic conditions, proton pump inhibitors are protonated and converted to cyclic sulphaniamides. These active covalently bind to H+/K+-ATPase and consequently irreversibly inhibit the activity proton pump.1

Common Side Effects of PPIs

- Headache
- Nausea
- Abdominal pain
- Vomiting
- Diarrhoea
- Dizziness
- Rash
- Anaemia
- Arthralgia's

And some of the less observed side effects are alopecia, upper respiratory tract infection, abnormal vision, hypomagnesia. As per the recent times ppi's have obtained negative publicity due to improper and long term use which may lead to severe adverse effects such as vitamin/mineral absorption ,bone fractures , pneumonia, clostridium induced diarrhoea and gastric polyps. This is not to deter the use of ppi's but to have a safe and proper use ppi.[2]

Objective of the Study

The main objective of the study is that mostly, each and every prescription now a day is the combination of one or more PPIS for any of the disease conditions that might be the prophylactic therapy or the standard treatment. But while prescribing any of the drug there is need of following proper treatment regimen guidelines, but this is not followed and the treatment is continued for longer duration's. Due to the use of these drugs for longer time there are chances of drug induced diseases. This study is the over view of all the Proton pump inhibitors induced diseases.

PPI's Induced Diseases

PPI's induced mineral and electrolyte absorption: Several animal and human studies support the conclusion that gastric acid secretion can affect the absorption of several nutrients, vitamins, and drugs. The effect on absorption of vitamin b12, iron, calcium, and magnesium has received particular attention recently because of the widespread maintenance use of proton pump inhibitors (ppi's) and h+k+atpase inhibitors (omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole), which are potent acid suppressants.

Effects on Vitamin B12 Absorption: It is well established that gastric acid secretion is needed for dietary vitamin B12 (VB12) absorption. The presence of gastric acid is needed for the pancreatic proteases to cleave the VB12 from the protein allowing its re association with intrinsic factor and eventual absorption in the terminal ileum.[5]

Mechanism: PPIs are the most potent inhibitors of gastric acid secretion, with a potential to increase intragastric pH by several units, as well as hydrogen ion concentration by several hundred to thousand fold. Their mechanism of action centres on inhibition of the H^+/K^+ ATPase enzyme in gastric mucosal parietal cells, which is responsible for hydrogen ion secretion in exchange for potassium ions in the gastric lumen. As a result, PPIs can modify the bioavailability and absorption of essential vitamins and minerals both in the stomach and duodenum.[5]

Treatment: Low B12 levels may require supplementation with oral tablets, sublingual tablets or fortified foods. If B12 levels do not normalize with oral supplementation, vitamin B12 is available as a monthly injection that bypasses gastrointestinal absorption.

Effects on Calcium Absorption: PPIs affect the body's ability to absorb calcium from the diet, as well as from calcium supplements. By lowering the stomach acid levels, the ability to digest the calcium and adequately absorb it into the body is decreased. Once the blood calcium levels are low, the body will attempt to correct this imbalance by taking calcium from the bones. The longer the body is low on calcium, the more calcium will be removed from the bone. This chain of events can lead to osteoporosis and bone fractures.

Mechanism: An acidic environment in the stomach facilitates the release of ionized calcium from insoluble calcium salts, and calcium solubilisation is thought to be important for calcium absorption. Several conditions that cause hypochlorhydria or achlorhydria, it is assumed that these conditions are secondary to the effect of low gastric acid levels on calcium absorption. Experimental evidence indicates that PPIs also may potentially influence bone resorption by inhibiting the osteoclastic proton transport system, thus ameliorating the negative effect of PPIs increasing the occurrence of osteoporosis by decreasing calcium absorption.[6]

Treatment: Calcium Citrate is the best option for calcium supplementation for patients currently on a PPI. Calcium citrate does not require an acidic environment to absorb the calcium in the digestive tract, while calcium carbonate does require stomach acid.[2]

Effects on Iron Absorption: Iron is an important part of many proteins and enzymes. In addition it is an essential component of oxygen transport in the blood. Iron digestion and absorption can be affected by PPI usage.

Mechanism: Like other vitamins and minerals, iron (specifically non-heme iron, 66% of iron found in food), has markedly decreased absorption in the absence of gastric acid. Patients undergoing long term suppression of gastric acid may be at risk for low iron levels so it is important to have your iron levels monitored. Gastric acid helps the food sources containing non-heme iron to dissociate and to solubilize the iron salts, allowing their reduction to the ferrous state, which allows the formation of complexes with ascorbate, sugars, and amines, in turn facilitating absorption.

Treatment: Iron-bisglycine is available in products known as Ferrochels, and Hemagenics. Also, the possibility of iron by injection is available for patients not able to tolerate oral supplementation.[7]

Effects on Magnesium Absorption: Magnesium is an important mineral in the body used to maintain normal muscle and nerve function, and heart rhythm. In addition, magnesium supports the immune system and improves bone stability.

Mechanism: As mentioned magnesium intestinal absorption is achieved through both passive diffusion and an active transport system. Approximately 90% of magnesium is absorbed passively *via* Para cellular pathways between the enterocytes. Specifically, a constant fraction of ingested magnesium is absorbed by simple diffusion in such a way that absorption increases linearly with luminal concentrations. The Trans cellular active transport mechanism operates through transient receptor potential melastatin (TRPM) cation channels, in particular TRPM6, are composed of linked channel and protein kinase domains. These channels conduct divalent cations (magnesium and calcium) into the cell following the Trans membrane electrochemical gradient. TRPM6 is expressed along the entire gastrointestinal tract, in kidney, testis and lungs, it could be speculated that PPIs affect the enzyme and/or the channel functions of the active transport system either directly or *via* intestinal pH changes. Alternatively, susceptibility to reduced intestinal magnesium absorption could be attributed to TRPM6 mutations.

Treatment: Oral replacement is appropriate for patients with mild symptoms, while intravenous replacement is recommended for patients with severe clinical effects. Numerous oral magnesium preparations (magnesium oxide , magnesium dietary supplements, Magnesium citrate.) are available Intravenous magnesium sulphate ($MgSO_4$) can be given in response to cardiac arrhythmias, pre-eclampsia.[7]

PPI induced enteric infections: Enteric infections are defined as an infection of the intestinal tract and present with diarrhoea, abdominal discomfort, nausea, vomiting and anorexia due to PPI therapy due to small bowel bacterial overgrowth. Normally, gastric acid would destroy the majority of ingested bacteria and prevent infection. Only a few cases of infections in patients taking PPIs have been reported risk. Practicing proper hygiene, proper kitchen hygiene (cleaning surfaces and utensils after contact with raw meats) and avoiding

sick or infected individuals and frequent hand washing are all ways to avoid enteric infections.[8,9]

Salmonella Infections: Salmonella is an acid-sensitive microbe associated with consumption of eggs and poultry products and secondary to contact with cold blooded reptiles. Additionally, therapy with PPIs may facilitate Salmonella infection by drug effects on neutrophils, which are the predominant inflammatory cells against non-typhoid Salmonella enteric infection. PPIs may also enhance susceptibility to Salmonella by facilitating the effects of Salmonella on the tight junctions in the intestinal epithelium. PPI action on resident intestinal microflora, pro-inflammatory cytokines and other local mechanisms could influence the pathogenicity of strains of Salmonella.[9]

Diarrhoeagenic Escherichia Coli: Diarrhoea-producing E. coli strains show decreased survival at pH < 3.5.5 Strains of E. coli appear to be more acid stable .However, the minimum pH supporting bacterial proliferation is 4.4 for strains of E. coli. A high gastric pH created by PPIs may facilitate the pathogenesis of E. coli diarrhoea. More studies are needed to specifically determine the association of PPI use and susceptibility to the various diarrhoea-producing E. coli strains including enter toxigenic E. coli (ETEC), common in travellers, Shiga toxin producing E. coli (STEC), an important food borne pathogen, and entero aggregative E. coli (EAEC), an important cause of paediatric diarrhoea, travellers' diarrhoea and AIDS-associated diarrhoea.[8]

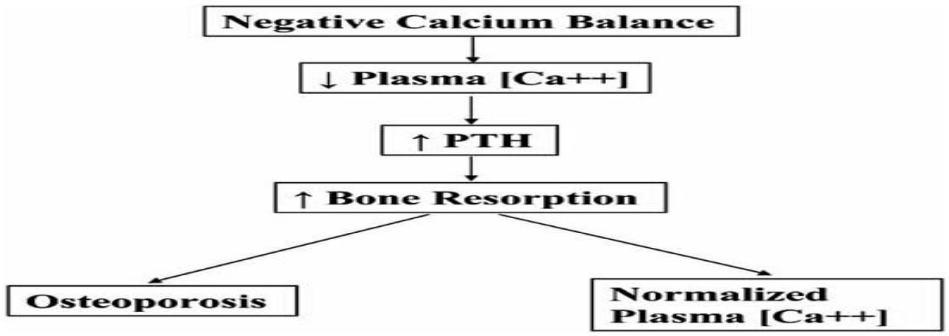
PPI Induced Dementia: Dementia is a progressive disorder characterized by deterioration in cognitive ability and capacity for independent living. It has a substantial and rising burden on patients, their families, and the healthcare system.

Mechanism: PPIs showed that they interacts with brain enzymes. They observed increased Aβ levels in an amyloid cell model and in the brain. They suggest a mechanism of inverse γ-secretase modulation in combination with an augmented β-secretase BACE1 activity that leads to an accumulation of Aβ levels. Aβ peptides are a major pathological sign of dementia in the course of Alzheimer disease. Another explanation for the enrichment of Aβ by PPIs might involve a modulation of degradation of Aβ by lysosomes in microglia.13Fibrillar Aβ clearance by microgliais pH-dependent, and this process is induced by acidification of lysosomes. Vacuolar-typeH+–adenosine triphosphatase (V-ATPase) proton pumps mediate this acidification, and PPIs have inhibitory properties atV-ATPases.15 As a result, PPIs may contribute to the inhibition of acidification, reduced Aβ degradation, and enhanced Aβ levels.

Treatment: Donepezil and other acetyl cholinesterase. Acetyl cholinesterase inhibitors (such as galantamine, and rivastigmine) are used to treat mild to moderate Alzheimer's disease. They can also be used to treat dementia with Levy bodies, and can be particularly effective at treating hallucinations.[10]

PPI Induced Osteoporosis: Osteoporosis is a disease characterized by low bone mass and deterioration of the bone architecture leading to increases fragility and fractures.

Mechanism: During chronic use of ppi's there occurs alteration in the mineral and electrolyte absorption as well as alteration in the calcium levels too. There occurs a negative balance in the body and in order to maintain homeostasis body reabsorbs calcium from skeletal system and in a long term the bones become fragile and cause fractures due to low mineral density.



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