Effect of Long Term Use of Proton Pump Inhibitor

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ABSTRACT
Proton pump inhibitors (PPIs), available with or without a prescription, are commonly used for the treatment of acid-related disorders. Despite their ease of availability and common use, PPIs can have severe side effects. The long-term consequences of chronic PPI use include the potential increased risk of hypocalcemia, hypomagnesemia, Clostridium difficile infections, and pneumonia. Community pharmacists are poised to provide evidence-based recommendations and educate patients about the benefits and risks associated with chronic PPI use.

Key Words: Proton pump inhibitor, Side effect, reduction of vitamins, Community pharmacists.

INTRODUCTION:
Proton pump inhibitor (PPIs) has been on the market since the late 1980s and has replaced the histamine-2 receptor-antagonists (H₂RAs) as the most potent class of drugs for the treatment of acid-related diseases. Anti-ulcer medications (therapeutic areas are based on proprietary IMS Health definitions) were the ninth largest class based on prescription volume in the United States in 2012 and the 11th in sales. Medications in the PPI class are widely available with or without a prescription. Currently, the U.S. market contains six PPIs, two of which are also available as OTC products. In the early 2000s, the FDA announced the availability of omeprazole (Prilosec OTC) as the first OTC PPI. It was soon followed by the approval of OTC lansoprazole (Prevacid 24HR). PPIs are used for the treatment of many gastric conditions including peptic ulcer disease, eradication of Helicobacter pylori infections, treatment and prevention of nonsteroidal anti-inflammatory drug (NSAID) gastroduodenal ulcer, Zollinger-Ellison syndrome, and gastroesophageal reflux disease (GERD). Generally, these medications are prescribed because of the low incidence of side effects and superior efficacy compared to other drugs used to treat the same conditions. Long-term use of any medication raises safety concerns, especially if that product is available OTC. The American Gastroenterological Association (AGA) released guidelines on the management of GERD in 2008 that...
recommended against routine monitoring for PPIs due to insufficient evidence. However, since then studies have continued to show long-term consequences from chronic PPI use including mal-absorption consequences and infections. Subsequently, in March 2013, the American College of Gastroenterology (ACG) released guidelines for the diagnosis and treatment of GERD. These guidelines do provide some insight into monitoring for long-term consequences of chronic PPI use. This article is a review of the recent literature and guideline recommendations regarding the possible long-term consequences of chronic PPI pharmacotherapy and opportunities to prevent these complications. In animal studies, PPIs raised concerns about a potential for hypergastrinemia, but human studies failed to show an association.

Therefore, long-term consequences of chronic PPI use can be grouped into two main categories, malabsorption and infections. Malabsorption secondary to PPI use affects calcium and magnesium, and the literature specifies two infections most often associated with PPI use, Clostridium difficile and pneumonia. Unfortunately, a definition in the literature for "long-term" is lacking; neither the AGA guidelines nor the ACG guidelines define what is considered long-term. For the rest of this article, the authors use long-term to designate therapy greater than 14 days, the maximum therapy for the OTC products.

MECHANISM OF ACTION:
The gastric H,K-ATPase is the primary target for the treatment of acid-related diseases. Proton pump inhibitors (PPIs) are weak bases composed of two moieties, a substituted pyridine with a primary pKₐ of about 4.0, which allows selective accumulation in the secretory canaliculus of the parietal cell, and a benzimidazole with a second pKₐ of about 1.0. PPIs are acid-activated prodrugs that convert to sulfenic acids or sulfonamides that react covalently with one or more cysteines accessible from the luminal surface of the ATPase. Because of covalent binding, their inhibitory effects last much longer than their plasma half-life. However, the short half-life of the drug in the blood and the requirement for acid activation impair their efficacy in acid suppression, particularly at night. PPIs with longer half-life promise to improve acid suppression. All PPIs give excellent healing of peptic ulcers and produce good results in reflux esophagitis. PPIs combined with antibiotics eradicate Helicobacter pylori. dramatic morphologic changes from the resting status to the stimulated state. The gastric H,K- When activated by stimuli such as histamine and acetylcholine, the parietal cell undergoes ATPase, which pumps gastric acid, appears to be in cytoplasmic
tubular membranes in the resting state and then in the microvilli of the expanded secretory canaliculus in the stimulated state of the parietal cell. This morphologic change is proposed to result from fusion of cytoplasmic vesicles with the rudimentary microvilli to form the elongated microvilli of the expanded secretory canaliculus. The gastric H,K-ATPase moves from the tubulovesicles to the apical membrane in the canaliculus of the stimulated state and secretes gastric acid by an electroneutral, ATP-dependent hydrogen-potassium exchange. The enzyme uses extracellular K⁺ in order to secrete acid by the exchange of cytoplasmic hydronium with this K⁺. The cation reaches the luminal surface of the ATPase by insertion of K⁺ Cl⁻ (KCNQ1, Clic6) channels into the microvillus membrane.

![Diagram of Stomach Lumen](image)

Proton pump inhibitors (PPIs) block the gastric H,K-ATPase, inhibiting gastric acid secretion. This effect enables healing of peptic ulcers, gastroesophageal reflux disease (GERD), Barrett’s esophagus, and Zollinger-Ellison syndrome, as well as the eradication of *Helicobacter pylori* as part of combination regimens. This article reviews the structure and function of the gastric H,K-ATPase and the inhibitors of this enzyme, the PPIs.

**Efficacy of Inhibition of Acid Secretion:**

All of these drugs inhibit the gastric H,K-ATPase by covalent binding, so the duration of their effect is longer than expected from their levels in the blood. However, PPIs cannot inhibit all gastric acid pumps with oral dosing because not all pumps are active during the 90-minute half-life of the PPI in the blood. Because PPIs have a short half-life, only 70% of the pump enzymes are inhibited. It takes about 2 to 3 days to reach steady state inhibition of acid secretion. The pump protein has a half-life of about 54 hours in the rat (and probably in humans). Thus about 20% of pumps are newly synthesized over a 24-hour period, and there may be greater pump synthesis at night than during the day. In addition, bedtime administration of PPIs will not add to inhibition of nocturnal acid breakthrough, because the drug will have disappeared by the time nighttime acid secretion is evident. Assuming that about 70% of pumps are activated by breakfast and that the PPI is given 30 to 60 minutes beforehand, it can be calculated that steady state inhibition on once-a-day dosing is about 66% of maximal acid output. Increasing the dose has virtually no effect once optimal dosage has been reached. Increasing the dose frequency does have some effect; a morning dose and an evening dose before meals results in about 80% inhibition of maximal acid output.
To improve acid inhibition, the plasma half-life of the PPI must be increased. One means is to replace the benzimidazole with imidazopyridine, slowing metabolism and prolonging the half-life of the drug, as found with tenatoprazole. This PPI has an advantage in suppressing nighttime acid secretion, but its slow activation blunts its advantage for daytime acid suppression. An alternative approach was to synthesize a slowly absorbed derivative of omeprazole, which then increased the plasma half-life about threefold and produced a median pH of about 5 in initial studies.

**Stability of Inhibition of Acid Secretion:**
Reversal of inhibition of the ATPase can occur either by de novo synthesis or reduction of the disulfide bond between the PPI and the protein. A rationale for examination of reversal of covalent binding to the H,K-ATPase was provided by measurement of the half-life of pump protein biosynthesis in rats treated for 7 days with omeprazole, which was 54 hours, and the half-time of restoration of ATPase activity, 15 hours. Such data suggest a more rapid recovery of ATPase activity and acid secretion than would occur if only de novo biosynthesis was responsible for restoration of ATPase activity. In other experiments, the halftime of restoration of acid secretion in omeprazole-treated rats was 20 hours. An analysis of the rate of restoration of acid secretion in humans suggested that the half-time was 24 hours following omeprazole inhibition, whereas after pantoprazole it was 46 hours. Only pantoprazole appears to have a rate of recovery compatible with restoration of acid secretion due entirely to pump turnover.

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**THE USE OF PPIS IS NOT ASSOCIATED WITH AN ALTERATION OF GASTRIC HISTOLOGY:**
In *Helicobacter pylori* (*H. pylori*) negative persons PPIs do not worsen pre-existing gastritis, and may even improve pre-existing gastritis. PPIs do not cause atrophic gastritis. In contrast, in *H. pylori* positive persons, *H. pylori* is associated with antral or body acute or chronic gastritis, atrophy and metaplasia. *H. pylori*-associated chronic gastritis may progress to gastric atrophy, intestinal metaplasia, and gastric cancer or may not. *H. pylori* and PPIs may cause progression or acceleration from gastric antrum-predominant chronic gastritis to body-predominant chronic gastritis, and it is controversial whether gastric body-predominant atrophic gastritis (gastric atrophy) is a risk factor for gastric cancer. *H. pylori* eradication may cause regression of gastric atrophy or intestinal metaplasia or may not.

Thus, the long-term use of PPIs has not been convincingly proven to cause or accelerate the progression of pre-existing chronic gastritis, corpus gastric atrophy or intestinal metaplasia.

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**THE USE OF PPIS IS ASSOCIATED WITH THE DEVELOPMENT OF FUNDIC GLAND POLYPS:**
PPI use is associated with parietal cell hyperplasia, and an up to fourfold increased incidence of fundic gland polyps (FGP). FGP also occur in the presence of *H. pylori* infection, likely incidentally. Eradication of *H. pylori* is associated with a...
pylori or stopping long-term use of PPIs is associated with regression of FGP. FGP in sporadic cases is rarely associated with dysplasia, but never gastric adenocarcinoma. Dysplasia may occur in 25%-44% of gastric polyps in persons with familial adenomatous polyposis. In summary, PPI use is associated with the development of FGP. FGP occur in the presence or absence of H. pylori infection. The eradication of H. pylori or stopping PPI is associated with regression of FGP. FGP may rarely become dysplastic, but almost exclusively this rare event is seen in persons with familial adenomatous polyposis.

PPIs may mask the symptoms of gastric cancer (GC), heal malignant gastric ulcers, or shorten survival in the patient with GC.

PPIs may mask the symptoms or heal early GC, but there is no data on the effect of PPIs on rates of survival. H2RA’s may or may not actually produce longer survival in patients with GC.

**BIOAVAILABILITY OR METABOLISM OF A FEW OTHER DRUGS:**

PPIs reduce gastric acid, and thereby reduce the bioavailability of drugs requiring intragastric acidity to maximize their absorption and bioavailability. Examples of such drugs would include ketoconazole, itraconazole and indinavir and may reduce the effects of locally acting drugs such as sucralfate.

PPIs may alter the intestinal first pass metabolism or the hepatic clearance of some drugs, and thereby modify their pharmacodynamics. They have no effect on n-acetyl-transfer or xanthine oxidase activities and may show a rare class action effect on vitamin K antagonists. PPIs have a low drug interaction through phase I/II effects and may differ in their possibility of causing drug interactions. Omeprazole and lansoprazole have a high affinity for CYP2C19 and CYP3A4 but these cytochromes contribute little to rabeprazole metabolism. Pantoprazole is completely metabolized by these cytochrome enzymes, but it uniquely has no drug interactions with a wide range of drugs.

**THE USE OF PPIS AND DEFICIENCIES IN IRON AND VITAMIN B12**

**Iron**

PPIS reduce gastric acidity, and in patients treated long-term with high dose PPIS duodenal absorption of organic and non-organic iron may be reduced. This effect however is small, and PPIS are not associated with an increased risk of latent iron deficiency or iron deficiency.

**Vitamin B12:**

PPIs reduce gastric acidity, which is necessary to activate pepsinogen to pepsin to release vitamin B12 from B12-containing foods. PPIs used short-term may minimally reduce the absorption of protein-bound B12 in food. In elderly patients who may already have gastric atrophy (possibly from H. pylori infection), PPIs used...
long-term may reduce serum vitamin B12 concentrations. Five out of six studies have shown that PPIs used long-term in non-elderly patients do not reduce serum vitamin B12 concentrations, and therefore body B12 stores.

In ZES patients treated long-term with high dose PPIs, the serum concentration of vitamin B12 may be reduced. And yet, in cystic fibrosis (CF) children with reduced secretion of pancreatic bicarbonate and increased duodenal acidity, there is no reduction in the intestinal absorption of B12.

Thus, long-term use of PPIs does not lead to vitamin B12 deficiencies, except possibly in the elderly or in persons with ZES who are on high doses of PPI for prolonged periods of time. Another proposed adverse effect of long-term PPI use is cobalamin malabsorption. Several mechanisms have been proposed by which PPI use may lead to cobalamin malabsorption. First, a more basic gastric environment may slow the release of cobalamin from dietary food sources.49 Another potential mechanism involves the risk of bacterial overgrowth that can result from PPI use. The excess bacteria in the small intestine may consume cobalamin before it can be absorbed.49, 5’- Yet another mechanism of decreased cobalamin absorption involves the theoretical possibility that PPIs could reduce intrinsic factor secretion by inhibiting parietal cell proton pumps; however, this has not been found to occur in actual practiced Overall, studies have shown that acid suppression may decrease vitamin B12 absorption, and with long-term use, may result in reductions in serum B12 levels.49,54 However, questions still remain regarding whether patients may develop clinical vitamin B12 deficiency as opposed to simply exhibiting reductions in serum levels that are still within the normal range.49’54 a particularly vulnerable population would be older adults, who are already at risk for cobalamin deficiency. Vitamin B12 deficiency can have significant consequences such as the development of dementia or neuropathy. Such conditions may not fully reverse, even with repletion. 1) With regard to the geriatric population, adults over the age of 65 years are estimated to have a 5-15% prevalence of B12 deficiency. 2) The etiology for B12 deficiency in older adults is thought to be related to malabsorption of dietary B12. This malabsorption may be from atrophic gastritis, age related hypochlorhydria, or other conditions such as H. pylori infection. It can take months to years for a B12 deficiency to manifest secondary to malabsorption because liver stores of B12 can compensate for decreased dietary intake.

RISK OF OSTOPENIA, OSTEOPOROSIS AND WITH BONE METABOLISM:

PPIs alter osteoclastic vacuolar mechanisms which may reduce bone absorption and thereby actually reduce the risk of OP. PPIs have no known adverse effect on vitamin D absorption or metabolism. The real question is whether PPI use is associated with an increased risk of osteoporosis/osteopenia, and more importantly with bone fractures. In case controlled studies, PPI use long-term is associated with an increased risk of bone fractures, and this increased risk depends on the duration and dose of chronic use of the PPI(e.g. Manitoba Population Health Research Data Repository).Use of PPI ≥ 5 years can increase the risk of osteoporotic fractures by 1.62-fold (95% CI: 1.02-2.58). Other studies confirm that use of PPI ≥ 7
years increases the risk of osteoporotic hip fractures by 4.55-fold (95% CI: 1.68-12.29) and PPI use for 6-12 mo has been reported to be associated with an increased risk of osteoporotic hip and spine fractures.

**COMMUNITY ACQUIRED NOSOCOMIAL PNEUMONIA:**

PPI use is associated with increased intragastric aerobic bacteria, and with the production of acetaldehyde from alcohol. The increased bacterial colonization of the stomach observed with PPI users may be associated with pulmonary micro-aspiration and lung colonization. In addition, it is postulated that secretions from the oropharynx may pass by micro-aspiration into the lower lung airways. Furthermore, lung colonization may occur as a result of mechanisms other than micro-aspiration of gastric contents, because different organisms may grow from cultures of gastric juice and from bronchoalveolar lavage.

In contrast, PPIs do not increase the risk of hospital acquired (nosocomial) pneumonia (NP). In fact, there is a reduced risk of NP in patients with nasogastric tubes on a PPI. For ventilated pediatric patients in ICU, there is no increased risk of NP.

Thus, short-term PPI use increases the risk of CAP, but PPI use does not increase the risk of hospital acquired pneumonia.

**CLOSTRIDIUM DIFFICILE-ASSOCIATED PNEUMONIA:**

There are numerous risk factors for CDAD (use of antibiotics, age, contact with an infected patient or healthcare worker, crowding, lack of cleanliness, post-pyloric tube feeding, patient immunosuppression). These factors must be taken into account for the attribution of risk, e.g. before assigning a possible role to a new factor, such as PPIs. Some observational studies show an association between PPI use and risk of CDAD. For example, for PPI use and CDAD in chronic renal failure patients, the AOR is 5.7 (95% CI: 1.3-39.1) (P = 0.02). In meta-analyses of studies of CDAD and PPIs, the AOR is 1.96 (95% CI: 1.28-3.00). Some of these reports involve a hypervirulent strain of *C. difficile*, and after correcting for other factors such as antibiotic use, there is no association with PPIs. H2RAs and PPIs create a hypochlorhydric to achlorhydric environment in the gut, thereby facilitating survival of certain ingested pathogens that would otherwise be killed by unaltered pH gastric juices. Regurgitation of ingested bacteria into the oropharynx can precipitate respiratory infections.

Current use of a PPI did not have an increased risk for CAP. PPIs take approximately seven days to yield maximum acid-suppressive effect. It is hypothesized that aspiration of pathogens into the hypochlorhydric to achlorhydric environment in the gut can predispose a patient to CAP. As Sarkar et al noted, intuitively, one would predict that those patients who have been taking PPIs chronically would be the most at risk of developing CAP. Overall, studies suggest that there is a modestly increased risk of developing CAP related to current or recent use of PPIs. However, some feel that the association of PPIs with CAP may result from the confounding presence of the underlying condition, namely GERD, and not PPI use itself.
Perhaps those patients with more severe reflux are at higher risk for aspiration and subsequent CAP regardless of their use of an acid-suppressive agent.

**SMALL BOWEL CONTAMINATION SYNDROME AND ENTERIC INFECTIONS:**

It is thought that PPIs have a minor effect on altering the intestinal bacterial microbiota. Observational studies have suggested that PPIs may or may not increase risk of enteric infections. Thus, PPIs do not have a convincingly proven adverse effect on the enteric microbiota, and if such an effect does exist, there is no proven clinically important adverse effect. The use and subsequent withdrawal of PPIs may be associated with an exaggeration of, or new onset of, acid-related symptoms. PPIs are a medication that is generously prescribed for a variety of symptoms that are thought, and not necessarily confirmed, to be acid-induced. One reason for this is the relatively low number of adverse effects that have been shown in the short- or long-term. One study suggests that symptoms that commence following the discontinuation of PPIs due to rebound acid hypersecretion may be as troublesome as the symptoms that the PPIs were being used to treat in the first place. Because of these rebound symptoms, there may be a need for further and continuous PPI use. As with all medications, the key is to use PPIs only when clearly indicated, and to reassess continued use so that long-term therapy is used judiciously. The risk of false-negative urea breath tests (UBT) for the diagnosis of an *H. pylori* infection is lower for pantoprazole. While it is recommended that acid suppression therapy should be discontinued prior to a UBT, the false-negative effect is lower for pantoprazole. The biological plausibility is poor for the possibility that PPI use is associated with an increased risk of colorectal cancer or adenomatous polyps, and there is no clinical data to suggest this possibility.

**CONCLUSION:**

Understanding the possible harms of commonly prescribed medications such as PPIs becomes paramount, particularly in the elderly, where issues such as polypharmacy and medication adverse effects and interactions are commonly encountered. PPI use is clearly indicated for certain conditions such as active peptic ulcer disease or stress ulcer prophylaxis in high-risk patients. However, when these conditions are not present, discontinuation of PPIs should be considered. While it is clear that PPI therapy is beneficial when used appropriately in the treatment of various GI disorders, growing evidence suggests that PPI therapy may be associated with several adverse outcomes, including C.diffi-cile infections, CAP, hip fractures, B12 deficiency, and possibly IgE-mediated allergic reactions. Such associations appear modest, yet data are limited by study size and/or design. Further studies are needed to explore the true relationship of PPIs to these outcomes.
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