Potential Adverse Effects of Long Term Use of Proton Pump Inhibitors

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Abstract

Proton-Pump Inhibitors (PPIs) have changed the therapy of numerous upper GI tract disorders; but their use is not without risk of adverse effects. Recent studies suggest more serious adverse events with chronic use of PPIs. Because of these risks, clinicians should reassess individual patient's needs for chronic PPI therapy.

Keywords

Proton Pump Inhibitors, Side effects, Osteoporosis, Clostridium difficile, Myocardial Infarction

Introduction

Proton-pump inhibitors (PPIs) are a widely used first line and evidence-based therapy for upper gastrointestinal (GI) disorders, including dyspepsia, peptic ulcer disease, gastroesophageal reflux disease (GERD), *Helicobacter pylori* (*H. pylori*) eradication therapy, lesions caused by nonsteroidal anti-inflammatory drugs (NSAIDs), stress-related mucosal bleeding, Zollinger–Ellison syndrome, and other hypersecretory conditions. PPIs are usually available as acid resistant, delayed-release, enteric coated capsules or tablets to protect them from destruction in the stomach. The orally administered prodrug is absorbed after the coating dissolves in the alkaline intestinal lumen. Common proton pump inhibitors include: omeprazole (Prilosec), lansoprazole (Prevacid,Prevacid 24 hour), dexlansoprazole (Dexilent,Kapidex), rabeprazole (Aciphex), pantoprazole (Protonix), esomeprazole (Nexium) and Zegarid, a rapid release form of omeprazole with sodium bicarbonate.

PPIs are metabolized into irreversible inhibitors of active proton pumps in gastric parietal cells; however, since not all proton pumps are active at the same time, not all are susceptible to inhibition. Approximately 70% of proton pumps are active in the morning and therefore most susceptible to PPI inhibition at this time. To allow for conversion of pro-drug into the active form, PPIs should be administered 30 to 60 minutes prior to meals, preferably breakfast.[1] PPIs interfere with both fasting- and meal-induced HCl secretion because they inhibit the final step of the HCl secretory pathway. Despite a relatively short half-life (usually 0.5–2 hours), PPIs have a lasting inhibitory effect on HCl secretion (between 48–72 hours) because of their irreversible binding to the H^+K^+-ATPase. Continuous treatment markedly decreases 24-hour HCl output and acidity of gastric contents. The inhibition of HCl secretion is progressive, and as a result, long term treatment with PPIs can lead to therapeutic hypochlorhydria, a deficiency of gastric HCl.

A majority of reviews, meta analyses, and evidence-based guidelines for management of acid-related disorders now favor PPIs over histamine H2-receptor antagonists (H2RAs) for most indications[9] because PPIs show high efficacy, are well tolerated, possess a desirable safety profile, and are affordable with both trade name and generic preparations available.[2,3] However, concern now exists because of frequent chronic off-label use at excessive dosages. Potential hazards associated with this misuse are discussed in this review.

Overutilization of PPIs

Although PPIs have been available in the United States since the mid-1980s[6,7], their use increased markedly following their approval as OTC agents in the early 2000's. This

availability, coupled with generic versions, a high prevalence of GERD, functional dyspepsia, and/or drug-induced upper GI lesions predominantly caused by NSAIDs all have led to markedly increased PPI use in ambulatory and clinical care settings.[4,5] The use of omeprazole, esomeprazole, and pantoprazole increased largely over the years 2002–2009 in the outpatient setting in the United States, and PPIs were prescribed in 4% of outpatient visits in 2002.[10] According to IMS Health data (National Prescription Audit), the number of prescriptions for PPIs increased from 146 million in 2009 to 164 million in 2013 (the 8th position on the list of the top therapeutic classes by prescriptions) and for omeprazole—from 46.6 million in 2009 to 70.7 million in 2013 (the 8th position on the list of top medicines by prescriptions). In many countries, PPIs have been among the top 10 best selling medicines for several years. In the U.S., their sales remain high, in excess of $10 billion per year.[8]

A growing body of literature now documents incorrect use and over use worldwide.[11,12] PPIs are frequently prescribed to patients at the time of hospital admission as "gastro protection" to reduce chances of litigation against physicians for negligent care.[13] PPI overutilization in the inpatient setting can be a result of stress ulcer prophylaxis (SUP) in non-intensive care unit patients and failure to discontinue SUP prior to hospital discharge. The overutilization of PPIs in ambulatory care settings is often a result of failure to re-evaluate the need for continuation of therapy, or insufficient use of on-demand and step-down therapy. In published research from Singapore, nearly half of 1025 patients (46.5%) hospitalized on a randomly selected day were administered PPIs, the majority of them (54.1%) without indications recommended by the Food and Drug Administration.[14] General practitioners also commonly prescribe PPIs for symptomatic treatment but without clear diagnosis or for unapproved indications. Interestingly, a recent analysis of data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey showed that 62.9% of outpatient visits by PPI users in the United States had no gastrointestinal diagnosis/complaints or other appropriate indications.[15]

Chronic PPI use is not without risks. These risks include colonization of microorganisms, including multi-drug resistant bacteria in the upper gastrointestinal tract, small intestine bacterial overgrowth, impaired gastrointestinal motility[16], impaired neutrophil function[17] and increased incidence of infections such as spontaneous bacterial peritonitis, *C. difficile* colitis, and pneumonia. In addition, patients with more advanced liver disease (who are more likely to be on PPIs) are also at higher risk of PPI accumulation due to impaired liver metabolism leading to extended pharmacokinetic effects and drug interactions.

The use of standard and often a double-dose of PPIs for initial treatment of upper GI tract symptoms has become ubiquitous, yet only a partial response to this therapy is observed in up to 30% of outpatients with GERD.[18] There is also evidence that many patients with GERD take excessive doses of PPIs chronically, although a double dose can be reduced to a standard dose in 80% of cases, and a standard dose may be reduced to a half dose in 58% of cases.[19] Although current guidelines recommend step down or on-demand strategies of treatment in selected GERD cases, some patients as well as clinicians seem reluctant to accept these instructions and some physicians continue pharmacotherapy with PPIs despite no evidence of GI pathology.

Patients who self-treat also often over-administer PPIs. The availability of these relatively inexpensive agents sold over the counter (OTC) could be one contributing factor to overutilization by outpatients. In addition, patient confusion between capsules containing a double standard dose (40 mg) of omeprazole with a standard dose of pantoprazole (40 mg)

can result in over administration. The lack of professional consultations prior to introduction of treatment and lack of medical supervision during pharmacotherapy are contributing factors for the overuse of PPIs in outpatients. GERD patients receiving PPI guidance and prescriptions from gastroenterologists were found to be more likely to be optimal users and achieve better symptom control than OTC consumers who used PPIs inappropriately and had inadequate GERD control.[20]

PPIs when taken short‑term have an excellent safety profile, with extremely rare clinically relevant adverse effects. The frequency of the most common side effects is only somewhat higher than placebo (< 6%).[21] Headache, the most frequent complaint in clinical trials, is declared by up to 5.5% of the subjects, and serious adverse reactions, such as hepatitis (lansoprazole, omeprazole), interstitial nephritis (omeprazole), or visual disturbances, which usually follow rapid intravenous infusion (omeprazole, pantoprazole) are rare.[22,23] However, extensive and unnecessary PPI therapy has led to hypergastrinemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy, leading to rebound acid hypersecretion. PPIs have also been linked via retrospective studies to increased risk of enteric infections including *Clostridium difficile*-associated diarrhea[24], community-acquired pneumonia[25], bone fractures[26], interference with metabolism of the antiplatelet agent clopidogrel [27] and more recently, with kidney disease[28], dementia[29] and myocardial infarction[30].

Clostridium difficile overgrowth

Clostridium difficile is the etiological agent for almost all cases of pseudomembranous colitis and 15-25% of antibiotic associated diarrhea. Acid-suppressive therapy has been suggested as a risk factor for *C difficile,* but its role remains controversial.[31] The incidence and severity of *Clostridium difficile* infections are increasing and they are associated with significant morbidity and increased length of hospitalization. *C. difficile* is the third most common cause of infectious diarrhoea in older patients seen by general practitioners[32] and the incidence of *C. difficile*–associated disease (CDAD) is now reported at 1.5% of outpatients in France yearly[33].

Gastric acidity is a major defence mechanism against ingested pathogens, and the PPI-associated loss of normal stomach acidity can lead to microbial colonization of the normally sterile upper GI tract.[34] Decreased gastric acidity following PPI use may result in insufficient eradication of ingested pathogens through several mechanisms including the alteration of gut micro flora, enhanced bacterial translocation, and alterations of various immunomodulatory and anti-inflammatory effects.[35] To understand the effects of PPIs on CDAD, attention has focused on the survival of acid-resistant spores, delayed gastric emptying, possible effects of bile salts, and roles of potassium and phosphate in gastric juice.[36] An accentuation of these PPI effects by *H. pylori* infection may account for the increased colonization risk in the elderly. The increase in CDAD infection in the past few decades has coincided in time with increasing use of PPIs, although other factors such as more virulent C. *difficile* strains may also play a part.[37]

The PPI-induced increase in gastric pH also affects leukocyte function[38], which may contribute to the reported associations between PPI use and increased risk of hospital- and nursing home–acquired CDAD[39,40]. Patients with continuous PPI use remained at elevated risk of *C. difficile* infection (CDI)[41] and one meta-analysis showed that despite heterogeneity among the studies, the risk of *C. difficile* infection was greater with PPIs than with H2 receptor antagonists[42]. Other enteric infections including Campylobacter[43], Giardia[44] and

Salmonella are also associated with excess PPI use although the magnitude of risk is unclear[45].

Collectively, retrospective literature indicates that PPI therapy is likely to increase the risk of *C. difficile* growth, though this must be confirmed through prospective studies. A decision to prescribe or continue PPI therapy must carefully weigh risks and benefits, particularly in high-risk situations such as hospitalized patients co-administered antibiotics, during institutional outbreaks, in elderly or immunosuppressed individuals, and in those embarking on travel to areas of risk for *C.difficile diarrhea.*

Bone and Calcium

In 2011, the FDA issued safety warnings concerning the risk of fractures of the hip, wrist and spine associated with use of PPIs.[46] As with many rare adverse effects, the risk was not recognised in randomized controlled trials prior to post-marketing epidemiological studies. The most recent meta-analysis of observational studies (mostly conducted in postmenopausal women and older men) found the risk of hip fracture and spine fractures up to 30% and 56% accordingly with high dose and long-term use (>1 year).[47]

The mechanism for the increase in fracture risk does not appear to be associated with either existing osteoporosis or accelerated bone mineral density loss and it remains largely unexplained.[48]As discussed by Targownik et al, PPIs might increase fracture risk by blocking the repair of micro-fractures and ultimately weakening bone strength.[49] Although the risk is only marginally higher than that in control populations matched for age, physicians should consider the presence of additional bone weakening risk factors such as corticosteroid use or pre-existing osteoporosis before prescribing PPIs.[50]

Rebound hydrochloric acid hypersecretion

Rebound acid hypersecretion (RAHS), defined as an increased HCl secretion above pre-treatment levels following antisecretory therapy, is one of the most important suggested theories for consumer overutilization of PPIs.[51,52] Niklasson et al showed that RAHS was observed in healthy volunteers taking a PPI in randomized, double blind study, and they suggested a class effect of these drugs.[53] It is believed that chronic PPI therapy results in a compensatory elevation in serum gastrin concentration and a secondary increase in parietal and enterochromaffin-like (ECL) cell mass and activities.[54,55] The withdrawal of PPIs then may lead to rebound acid secretion and acid-related symptoms in the upper GI tract such as heartburn, acidic regurgitations, or dyspepsia. These symptoms then lead patients to return to PPI therapy. RAHS is observed within 14 days after discontinuation of pharmacotherapy and the duration of RAHS may correlate with the duration of PPI therapy.

RAHS may lead to “PPI dependency” in which rebound symptoms cause anxiety and decrease the quality of life to such an extent that patients wish to ameliorate the symptoms immediately (“PPI withdrawal syndrome”). The patient, unaware of the pathogenesis and temporal nature of RAHS, could seek professional help, but with limited access to specialists, such as gastroenterologists, they often turn to readily available OTC PPIs. Such a scenario leads to an overuse of PPIs as well as increased treatment costs, risk of chronic HCl suppression, and “pseudo tachyphylaxis” due to an increased total mass of the parietal cells.

Hypergastrinemia and its consequences

Hypergastrinemia follows treatment with all PPIs, although some data claims that this increase may be lower with omeprazole than with rabeprazole[56] and lansoprazole[57] and lower with pantoprazole than with omeprazole[58], but the differences seem to be clinically irrelevant. Gastrin, released by G cells of the stomach, duodenum, and the pancreas, is a fundamental stimulus for postmeal HCl secretion. This peptide hormone stimulates mitosis, synthesis of DNA, RNA, and structural proteins of cell membranes; therefore, an increased serum gastrin concentration in long-term users of PPIs raises theoretical concerns about prolonged effects of hypergastrinemia. Although PPIs are regarded as safe pharmaceuticals, this secondary hypergastrinemia raises concern because of the risk of gastrin-induced neoplastic transformation of the gastric mucous membrane.[59] No causative link has been proven between PPIs and gastric cancer; however, a correlation between hypergastrinemia and ECL cell hyperplasia has been reported in humans and in the last 20 years, the incidence of carcinoids has increased.[60] At present, the routine monitoring of serum gastrin concentrations is not recommended in patients on long term PPI treatment.[61]

Chronic acid suppression in *H. pylori* positive patients may in theory promote chronic gastritis in the gastric body that precipitates atrophy and intestinal metaplasia as well as increases the risk of gastric adenocarcinoma. But no evidence indicates that acid suppressive pharmacotherapy increased the risk of carcinoma at any site in humans and, in fact, PPI therapy is safe for patients with Barrett's oesophagus.[62] One study in rats suggested that omeprazole may act as a liver tumour promoter, a finding which certainly deserves follow-up in other animal models.[63] The strongest risk association of PPI use and malignancy may be that PPI use can mask the symptoms of early gastric cancer and therefore delay an accurate diagnosis and treatment.

Fundic gland polyps

PPI use is associated with an increased incidence of fundic gland polyps (FGPs), mainly in *H. pylori* negative patients on long-term PPI treatment.[64] In a study by Zelter et al, PPI use was the most important risk factor for the presence of FGPs.[65] Although chronic pharmacotherapy with PPIs increases the risk of FGPs four fold, FGPs still only develop in a small number of PPI users.[66] Interestingly, the level of PPI-induced hypergastrinemia is not related to the development of FGPs.[67] PPI-associated FGPs are usually asymptomatic, small in size, and benign with low-grade dysplasia found in less than 1%.[68] Despite some case reports on high grade dysplasia within FGPs in non-familial adenomatous polyposis patients[69], FGPs are not considered a risk factor for gastric malignancies. Nevertheless, their presence on endoscopy may cause patients' distress and lead to unnecessary endoscopic and histological follow up. Discontinuation of PPIs may result in complete regression of FGPs.[70]

Pneumonia

Although early studies suggested a weak association between community-acquired pneumonia (CAP) and PPI use, systematic review of 26 studies including 226,769 cases of CAP observed a pooled risk of 1.49 with ambulatory PPI therapy. This risk was increased during the first month of therapy, regardless of PPI dose or patient age. PPI therapy also increased risk for hospitalization for CAP.[71]Current data do not indicate significant links with nosocomial or ventilator-associated pneumonias.[72] Furthermore, a retrospective analysis of the original safety data from several randomized clinical trials has shown that esomeprazole does not increase risk for CAP compared to placebo.[73] Reports of increased leakage via tight

junctions of mucosa caused by PPIs apply only to molecules in the 500–4000 Da weight range and not to larger molecules or particles, therefore this leakage phenomenon is unlikely to affect bacteria.[74]

Enteric malabsorption

Approximately 40 cases have been reported of proton-pump inhibitor (PPI)-induced hypomagnesaemia (PPIH).[75] In March 2011, the US Food and Drug Administration (FDA) issued a safety announcement, including hypomagnesaemia as a long-term side-effect of PPI use based on accumulating evidence.[76] The mechanism by which this occurs is still unclear. PPIs may decrease magnesium (Mg) absorption from the intestine by interfering with both active transient receptor potential melastatin (TRPM) protein channels as well as passive absorption.[77]

With long-term use of PPIs, clinicians should be aware of the PPIH-related presentations. These range from no symptoms to leg cramping, lethargy, seizures and arrhythmias.[78, 79] PPIH is usually recognized after five years of PPI use and short-term PPI use is not usually associated with hypomagnesaemia. Prompt removal of PPI and magnesium replacement can normalize Mg^{2+} levels and prevent re-hospitalizations and complications. The syndrome of HHHP (Hypomagnesaemic hypocalcaemic hypoparathyroidism) is usually associated with PPIH due to hypomagnesaemia interfering with PTH and Ca^{2+} homeostasis and should be considered in any presentation with cardiac arrhythmia, neuromuscular weakness or irritability.[80, 81]

PPIs inhibit secretion of hydrochloric and also ascorbic acids, which in turn, can markedly reduce the absorption of iron in its reduced form, particularly in the presence of *H. pylori* gastritis. However, there has been no documented association of PPI therapy with iron deficiency anemia.[82] PPI use has also been linked with the possible development of painful restless legs syndrome, long associated with iron deficiency and low serum ferritin concentrations. In the opinion of some researchers, iron deficiency is the most important potential adverse effects of PPI therapy, especially in patients who are poorly nourished, although this opinion requires support by future prospective studies.

Long-term therapy with omeprazole has been associated with vitamin B12 malabsorption[83] and it is reasonable to assess vitamin B12 levels periodically in patients who are on long-term treatment with PPIs[84].PPI inhibition of gastric acid secretion, pepsin, intrinsic factor, vitamin C and other substances have all given rise to concerns about a number of possibly resulting clinical deficiency states.

Food allergies and eosinophilic esophagitis

Many experiments show that several ingested potential food allergens, which are normally acid labile, become antigenic during PPI therapy due to increased gastric pH. Since PPIs also dose dependently increase mucosal permeability, small peptide antigens could be absorbed.[85] Treatment with PPIs for three months increases plasma IgE levels, new food-specific IgE and a mucosal immune response. One recent hypothesis proposes that PPIs may be responsible for eosinophilic esophagitis.[86]

Myocardial Infarction (MI)

PPI use is associated with elevated risk of MI in the general population; H2 blockers show no such association. The associations are independent of clopidogrel use, presence of acute coronary syndromes (ACS)[88] or patient age[87]. The mechanism for the cardiovascular risk is unknown, although recent in vivo data demonstrating that PPIs inhibit dimethyl arginine dimethyl amino hydrolase (DDAH) activity may be a contributing factor.[89] DDAH metabolizes asymmetric dimethyl arginine (ADMA), which is an endogenous and competitive inhibitor of nitric oxide synthase (NOS).[90] Increases in plasma ADMA levels of as little as 10% are associated with increased risk of major adverse cardiovascular events.[91, 92] PPIs increase intracellular ADMA in cultured human endothelial cells by approximately 30% and patients taking PPIs have increased serum ADMA levels.[93] These associations provide a possible pathway by which PPI usage deregulates vascular NOS, leading to increased risk of MI.

Acute and Chronic Kidney disease

PPI use is associated with acute kidney injury (AKI), most specifically, acute interstitial nephritis.[94] This injury occurs in only a small percentage of exposed persons and is not dose dependent, but it is associated with extra renal manifestations such as hypersensitivity. The injury usually recurs after re-challenge and might occur because the drugs act as haptens and elicit anti-membrane[95] antibodies.

PPI use may also be a risk factor for chronic kidney disease (CKD), potentially mediated by recurrent AKI[96] or by hypomagnesaemia (PPIH)[97] and with incident CKD[98]. One recent observational study shows that PPI use is associated with a higher overall risk of incident CKD. They are associated with incident CKD in both unadjusted and adjusted analysis for demographic, socioeconomic, and clinical variables and in comparison with H2 receptor antagonist users.[27]

Dementia

PPIs have a now-confirmed association with dementia as a recent study based on information from a pharmaceutical database has shown a significant risk of dementia with the three most often used PPIs, omeprazole, pantoprazole, and esomeprazole with a slightly increased risk of dementia by use of esomeprazole.[28]

The mechanism by which PPIs might influence the development of dementia is not understood and the association is epidemiologic at this time. Some PPIs (e.g., lansoprazole and omeprazole) can cross the blood-brain barrier potentially affecting neuronal targets.[99,100] Badiola et al mentioned increased Aβ levels in an amyloid cell model as well as in the brains of mice after PPI treatment.[101] Inverse γ-secretase modulation in combination with an augmented β-secretase BACE1 activity can explain accumulation of Aβ levels.[102] PPIs might also modulate the degradation of Aβ by lysosomes in microglia.[103] Fibrillar Aβ clearance bymicroglia is pH-labile and can be induced by acidification of lysosomes. Vacuolar-type H+ –adenosine triphosphatase (V-ATPase) proton pumps mediate this acidification, and since PPIs have inhibitory properties at V-ATPases[104], they could inhibit acidification, reduce Aβ degradation, and enhance Aβ levels[105]. Another possibility is suggested by Lam et al, in which PPI use in patients with poor vitamin B12 status has been described as leading to neurological damage by impaired DNA synthesis, methylation, and homocysteine neurotoxicity.[106,107,108]

Conclusions

PPIs have changed the therapy of numerous upper GI tract disorders; but their use is not without risk of adverse effects. Recent studies suggest more serious adverse events with chronic use of PPIs. Large, randomized, prospective trials are needed to more firmly establish direct cause and effect relationships between PPIs and adverse events in specific patient cohorts. Because of these risks, clinicians should reassess individual patient's needs for chronic PPI therapy. We should look for PPIs in patients' charts and should make a mark on prescribed PPIs which do not make sense. It is also reasonable to taper if it has been prescribed in higher than recommended dose. Limited course of PPIs followed by H2 blockers is worth to try to avoid long term use of PPIs.

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