REVIEW ARTICLE

Long-term effects of proton pump inhibitors

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Abstract

This review summarizes the literature regarding long-term adverse effects of proton pump inhibitors (PPIs). There is widespread use of PPIs for a number of indications both in the inpatient and outpatient settings. While PPIs are generally considered safe and well tolerated, more serious adverse events have been reported. The risk of pneumonia was increased 27–39% in short-term use of PPIs in three meta-analyses. The use of PPIs is associated with *Clostridium difficile* infection (CDI) and appears to be dose related. Fractures and the impaired magnesium absorption associated with the use of PPIs have led the FDA to issue a warning regarding their use. Thrombocytopenia, iron deficiency, vitamin B_{12} deficiency, rhabdomyolysis and acute interstitial nephritis (AIN) have also been reported with the use of PPIs. Even though these adverse effects occur in small percentage of people, their impact should not be underestimated. PPIs are widely used and even a rare adverse effect may result in a large number of people being affected. Practitioners need to be vigilant about such adverse effects and counsel patients accordingly and use PPIs only when indicated.

Keywords: proton pump inhibitors; pneumonia; *Clostridium difficile*

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Received 25 January 2015; *Revised* 19 March 2015; *Accepted* 26 March 2015;.Published.31.March.2015

Citation: Sethu Babu. Long-term effects of proton pump inhibitors. J Med Sci Res. 2015; 3(2):94-100. DOI: http://dx.doi.org/10.17727/JMSR.2015/3-019

Introduction

Proton pump inhibitors (PPIs) are medications that are ubiquitous in clinical practice and particularly in gastroenterologist's practice. This class of medication has been available for commercial use for nearly 25 years and this class of acid-reduction agents has supplanted the use of histamine-2–receptor antagonists (H_2RA) for patients with moderate to severe gastric acid–related diseases as well as for prophylaxis of upper gastrointestinal (GI) injury (e.g. with nonsteroidal anti-inflammatory drugs). Their safety among pharmacologic agents has been unparalleled as one of the safest class of medications that gastroenterologists deal with. However, there have been emerging concerns with reports of potential adverse effects associated with use of PPIs. The Food and Drug Administration (FDA) has issued a number of broad-based product warnings both for prescription and over-the-

counter purchase of most of the available PPIs. The pathogenesis of these proposed associations is not clear in most cases and the evidence base to support a clear association for harm is extremely variable. These potential interactions have ranged from alteration of absorption of vitamins and minerals, metabolic effects on bone density, alteration of pharmacokinetics/ pharmacodynamics, alterations of intended effect, increased infection risk and hypersensitivity response with consequent organ damage. This review examines the proposed scientific basis for the adverse events and the evidence base surrounding these controversies in clinical practice [1].

Overview of PPI action

The secretion of gastric acid is a complex and continuous process incorporating neuronal, paracrine and endocrine pathways. These separate signalling mechanisms converge at a common endpoint to promote the secretion of hydrogen ions by gastric parietal cells. Proton pumps are located on the plasma membrane of gastric parietal cells. They create an acidic environment in the gastric lumen by exchanging one hydrogen ion for one potassium ion via the H+/K+-ATPase pump. All PPIs are substituted benzimidazole derivatives that irreversibly inhibit the proton pump. Upon protonation to the active sulfonamide in the acidic secretory canaliculus, the drug covalently binds to the sulfhydryl group on the proton pump to prevent acid secretion into the gastric lumen. Acid secretion will resume only after a new proton pump is synthesized, after about 24–48 hrs.

PPIs are eliminated primarily via hepatic metabolism by cytochrome P2C19 and 3A4 while the renal elimination is negligible. Since proton pump inhibitors (PPIs) block acid secretion from all three pathways simultaneously, they are considered the most potent medications available to reduce gastric acid secretion. There are currently six PPIs available for use: omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole and ilaprazole. PPIs are indicated in the prevention and treatment of acid-related disorders. PPIs are indicated for relatively short-term use, up to 8 weeks for peptic ulcer disease, gastroesophageal reflux disease (GERD) and erosive esophagitis and up to 2 weeks for heart burn and *Helicobacter pylori* eradication. The efficacy, availability and ease of use of PPIs has led to its overuse in both outpatient and inpatient settings. The most common adverse effects include headache, nausea, abdominal pain, flatulence and diarrhea, which are usually mild and self-limiting. However, there are several serious potential adverse effects associated with long-term use [2].

Infections

Patients on long-term PPIs may be at an increased risk of infection. The hypothesis for the mechanism is that the gastric acid secretions act as a defence mechanism against enteric bacteria, and the increased gastric pH during PPI use allows for colonization of opportunistic microbes [3-5].

Clostridium difficile

In a retrospective study published in 2005, researchers found that patients who were taking PPIs had a hazard ratio (HR) of 2.9 for developing *C. difficile* infection; 75% of reported cases were more than 65 years of age. It was also observed that patients, who received a PPI during treatment of *C. difficile*, were 42% more likely to have a recurrent infection after completing therapy. In 2012, the FDA issued a statement detailing the relationship between *C. difficile*–associated diarrhea (CDAD) with the use of a PPI. The FDA safety alert warns patients and healthcare professionals to consider CDAD if a patient takes a PPI and experiences persistent diarrhea [6]. The FDA also recommends that patients to be started on the lowest dose of PPI for the shortest period of time to treat their current condition. The 2013 ACG guidelines recommend use of PPIs with caution in patients with a risk of *C. difficile* infections. In a pharmaco-epidemiological cohort study of 101,796 patients over a 5-year period, CDI also increased with the degree of acid suppression. Compared with patients who did not receive acid suppressive therapy, the risk of CDI was higher in patients taking a H2 receptor antagonist, a daily PPI or a PPI dose greater than once daily. Owing to the widespread use and over-the-counter availability of PPI, patients need to be counselled regarding the risk of CDI [7-10].

Community-acquired pneumonia (CAP)

Patients taking PPIs are potentially at increased risk for CAP. However, the degree of association is unclear due to conflicting data. The 2013 ACG guidelines states that short-term PPI use may

increase the risk of CAP, but the risk does not seems to be elevated in long-term use. PPIs were 2.23 times more likely to develop a CAP infection compared to patients not on PPIs. Unfortunately, the duration of time that patients were prescribed was not studied. In a meta-analysis completed in 2004, patients who were on an acid-suppressing agent, either a PPI or an H_2RA, were 4.5 times more likely to develop pneumonia. Mean duration of use for H_2RAs was 2.8 months and for PPIs the mean duration was 5 months. Conversely, a study conducted by Sarkar et al showed that current PPI use was not associated with an increased risk of CAP. However, the study did observe an increased risk of acquiring an infection in patients initiated on a PPI within the past 14 days. The data supports a short-term increased risk of infections, but there are conflicting results on long-term consequences. Despite the conflicting data, this risk is important to consider. In another study, Laheij et al. showed that the incidence of pneumonia was 2.5 per 100 patient-years for patients on PPIs. The cost of pneumonia hospitalizations, the risk of PPI use-associated infections warrants vigilance and evidence-based medical practice [11-13].

Risk of fractures

Long-term PPI use has been associated with an increased risk of osteoporosis and decreased bone mineral density (BMD), with a 35% increased risk of fractures [14]. If acid secretion is impaired, calcium salts are minimally ionized and as a result, calcium may not be properly absorbed. This may cause reduced levels of calcium and secondary hyperparathyroidism. Over time, this can lead to a reduction in bone mass, ultimately increasing the risk of bone fractures. Patients who received PPIs for 6–12 months were more likely to receive anti-osteoporotic medications compared to patients who received PPIs for less than 3 months. There are several epidemiological studies evaluating the association of PPI use and fracture risk. The majority of these studies show an association of PPI use and the development of fractures. The risk of hip fracture increased significantly with longer duration of PPI use; however, this was not consistently seen.

An analysis of the data obtained from the Canadian Multicentre Osteoporosis Study revealed that the use of PPIs was associated with lower BMD, particularly at the hip and femoral neck, when compared to non-PPI use [19]. However, long-term PPI use was not associated with an accelerated decline in BMD. A prospective trial of 1211 postmenopausal women offers additional evidence that PPI use is an independent risk factor for vertebral fractures. Risk of vertebral fractures was significantly higher for omeprazole users compared with nonusers. Recently, the US FDA issued a warning regarding PPI use and the risk of developing fractures. Patients may be at higher risk of developing fractures and this may be related to the dose or the duration of use of PPIs. If long-term PPI therapy is to be used, monitoring of bone density may be considered in selected patients, especially in postmenopausal women. The 2013 ACG guidelines on GERD state that existing osteoporosis is not a contraindication to PPI therapy. Patients with osteoporosis may remain on PPI therapy unless another risk factor for hip fracture exists [13]. However, several studies have demonstrated an association between long-term PPI use and risk of fractures, but there were many confounding factors. Common risk factors for fractures such as a sedentary lifestyle and concomitant use of certain medications (e.g. thiazide diuretics, hormone replacement therapy, corticosteroids) are often observed in patients who routinely take PPIs. Additionally, patients who take high doses of PPIs are at higher fracture risk versus patients who take lower doses. Finally, patients who take PPIs for extended periods of time (>1 year) are more likely to experience a fracture [16-19].

Effects on vitamin and mineral absorption

Iron

The absorption of Iron is related directly to the release of ferric iron by gastric juice. There is evidence suggesting that this process is related more specifically to the vitamin C released in gastric secretions, which acts as a reducing agent and prevents the formation of insoluble compounds. Although there is concern regarding evidence that PPIs may reduce the bioavailability of ingested vitamin C, long-term follow-up evaluation of patients taking chronic daily PPIs for up to 7 years has not shown iron malabsorption to be clinically apparent. Further, most cases of iron malabsorption can be managed clinically with the use of medicinal iron supplements that are absorbed independent of gastric acid and vitamin C. In Patients receiving chronic PPI therapy there was a significant decrease in all hematologic indices from baseline. Despite

these findings, there are limitations and studies did not offer a definitive answer on this issue. Although it is conceivable that PPI therapy may reduce absorption of non-heme iron and retard iron pool replenishment, this effect has not been well established or evident from widespread use in clinical practice [20].

Calcium

The absorption of dietary calcium is believed to be mediated by gastric acid release of ionized calcium from insoluble calcium salts. Hence, there have been concerns that hypochlorhydric states, in particular those induced by PPIs, may impair calcium absorption; however, there are limited data to support this claim. In 2010 the FDA issued a product label warning for all PPIs because of clinical reports inferring increased risk for bone fractures. The FDA revised this warning in March of 2011 to release over-the-counter PPIs, which are intended for short-term use (i.e. 2 weeks) for up to 3 cycles per year. Literature analysis of PPI use and bone fractures revealed conflicting results. The earlier published reports linking PPI use to the development of hip fractures were observational case-control studies and thereby have greater potential for bias and therefore less accurate estimates. Patients on PPIs have decreased levels of urinary calcium and hydroxyproline, suggesting decreased osteoclast activity and bone resorption. In addition, these patients have increased levels of the osteoblast precursors, osteocalcin and tissue-resistant alkaline phosphatase, suggesting new bone formation. There is no good evidence to establish that PPI use has a significant risk for bone density loss or osteoporosis related fractures. Accordingly, the data on bone density loss and osteoporotic fractures would not support that PPI therapy be discontinued in patients taking PPIs for appropriate indications at appropriate doses. Supplemental calcium is not recommended or justified solely because of PPI use [14, 21].

Magnesium

There are several case reports and case series in the literature documenting an association between PPIs and hypomagnesemia. Hypomagnesemia occurred after at least 3 months of PPI use, and often after a year or more. Resolution of hypomagnesemia occurred within about 1 week of discontinuation of PPI therapy. In cases of re-challenge, hypomagnesemia developed within a couple of weeks of re- initiation of PPI therapy. The patients generally presented with profound hypomagnesemia and typically required hospitalization. In approximately 25% of these cases, the patients had persistent hypomagnesemia despite supplements. Prompt resolution of magnesium levels was evident after discontinuance of the PPIs, and in a few cases in which the patients were re-challenged with a PPI, the hypomagnesemia recurred, suggesting a PPI-related effect. None of the patients had identifiable GI wasting or renal loss etiologies. The mechanism for the magnesium depletion is not known. The primary absorption of magnesium is through a passive pathway in the small intestine. However, there is some identifiable active transport via transport channels (transient receptor potential and magnesium transporter 6 and 7). It is not known if PPIs may have some effect on this pathway, but there are familial cases with mutations at this pathway who develop hypomagnesemia. PPI use was associated with a significant risk of developing hypomagnesemia when adjusted for confounding factors such as age, sex, diabetes mellitus, heart failure, diuretic use, electrolyte supplementation, acute gastrointestinal (GI) illness and laboratory values for serum albumin, potassium and serum creatinine. The FDA included a warning regarding PPI use and the risk of hypomagnesemia. Patients may be at higher risk of developing hypomagnesemia and related clinical manifestations that may be related to the duration of PPI therapy. Given the extreme rarity of the reports and no controlled studies to delineate the mechanisms, it is important for health care providers to be aware of this, but can use PPIs where clinically justified [22].

Thrombocytopenia

There is very little published data about the association between PPIs and thrombocytopenia. A retrospective cohort study evaluated 468 in-patients who received pantoprazole and 468 controls for the development of thrombocytopenia. No difference in the incidence of thrombocytopenia was found between the pantoprazole and control groups. The long-term use of PPIs and thrombocytopenia cannot be firmly established and it is unclear whether routine monitoring of platelet count is necessary [23].

Vitamin B_{12} deficiency

Gastric acid is involved in the absorption of B_{12} by facilitating its release from dietary protein, such that B_{12} can bind to R proteins. This B_{12}–R protein complex is broken down in the duodenum and, subsequently, B_{12} can be absorbed in the terminal ileum once bound to intrinsic factor. Because B_{12} absorption is dependent on gastric acid, theoretically, long-term PPI use may impair an individual's absorptive ability. Studies examining the potential relationship between PPIs and B_{12} have shown conflicting results and a prospective trial is needed to conclude any causative effect. In addition, to date no studies have provided a longitudinal evaluation showing alterations of specific metabolic intermediates (e.g. methylmalonate and homocysteine), which can accumulate with this deficiency. Further, because hypochlorhydria would only impair the release of B_{12} from dietary protein, absorption of oral B_{12} supplements should be unimpaired. Studies examining the potential relationship between PPIs and B_{12} have shown conflicting results, and a prospective trial is needed to conclude any causative effect [24].

Rhabdomyolysis

A large, retrospective analysis was completed using the WHO Collaborating Center Adverse Drug Reaction database to determine if previous reports of rhabdomyolysis could be associated with PPI use. Of the 292 cases of myopathies, 35 cases of rhabdomyolysis were identified from eight different countries. The onset of rhabdomyolysis ranged from 1 week to 10 years after PPI initiation. Of note, 12 of the 35 cases also received a 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor concurrently. PPI-associated rhabdomyolysis seems to be an extremely rare event that can occur at any time during PPI treatment, although the event seems to occur more frequently during the initial weeks of treatment. Pharmacists need to be vigilant about educating their patients regarding this rare adverse event of PPIs, especially if receiving combination therapy with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor.

Alteration of pharmacodynamics: Clopidogrel

PPIs are metabolized by the cytochrome P450 pathway, specifically CYP2C19 and CYP3A4. As a prodrug, clopidogrel requires a biotransformation to be converted into its active form, a process also mediated by the CYP2C19 and CYP3A4 enzymes. This reliance on the same pathway has led to the hypothesis that competition at CYP2C19 may reduce the biological activity of clopidogrel. This is an important consideration when analysing potential competition between PPIs and clopidogrel because these polymorphisms are quite prevalent, affecting 30% of whites, 40% of blacks, and 55% of East Asians. In January 2009, the FDA issued a recommendation against the combined use of clopidogrel and all PPIs, subsequently revising their statement to recommend against potent CYP2C19 inhibitors, naming omeprazole, esomeprazole, and cimetidine. This recommendation was based on several high-profile retrospective database evaluations that found higher cardiac event rates (stent thrombosis, myocardial infarct, and death) in patients who were taking clopidogrel with any PPI vs those on clopidogrel alone. In stark contrast, around this same time the leading clinical gastroenterology and cardiology national societies issued consensus recommendations supporting the combined use for patients at increased risk for GI bleeding. Despite the FDA's recommendation against specific PPIs, the most recent meta-analysis on the subject found no consistent evidence for intra-class differences among PPIs when used with clopidogrel [25]. Early studies suggested that pantoprazole, a less-potent inhibitor of CYP2C19, would have less effect on clopidogrel, and the current product labelling indicates no reduction of effect on concomitant dosing with clopidogrel. However, a recent placebo-controlled randomized trial showed a significant reduction on the antiplatelet effect. Despite this, combination therapy did not significantly increase the risk of adverse cardiovascular events. In fact, the most recent post hoc database assessment (using the Veterans Administration database) did suggest an apparent cardiovascular harm for combined use, but when the investigators used propensity-matched evaluations to correct for covariate cardiovascular risks and medication compliance, they found no significant association between major cardiovascular events and use of clopidogrel with continuous, switched or discontinued PPIs. In addition, a systematic review of 19 studies showed considerable heterogeneity. The studies did not allow for the demonstration of a clear interaction between clopidogrel and PPIs in platelet function studies. Given the lack of concise

randomized controlled trial data, appropriate assessment of the patient is the key consideration. For patients showing signs and symptoms of acid-related disease or patients meeting risk criteria for GI nonsteroidal anti-inflammatory drug injury prophylaxis, there is evidence to support the concomitant use of PPIs [26-30].

PPI in cirrhosis and chronic liver disease

Infections in cirrhosis, especially those associated with intestinal bacterial overgrowth and translocation such as spontaneous bacterial peritonitis (SBP), are responsible for a substantial cost of care and can increase mortality up to four-fold. These infections can impact patients directly by causing death or indirectly by precipitating hepatic encephalopathy and renal failure or reducing liver transplant eligibility. The leading pathogenic mechanism behind these infections in cirrhosis is small intestinal bacterial overgrowth (SIBO) leading to bacterial translocation, a process that is enhanced by acid suppression. Efforts to reduce this tremendous burden in cirrhosis by potentially reducing the bacterial translocation and overgrowth are needed. Decompensated cirrhotics who were started on PPI therapy after decompensation had a significantly higher risk of developing serious infections compared with those who were not initiated on gastric acid suppression. This increase in risk occurs in a time-varying fashion and is not explained by confounding by concomitant drug use, comorbid conditions or age. As patients with decompensated cirrhosis remain at a high risk of serious infections, clinicians should re-evaluate the reason for prescribing PPI and wherever possible, replace their acid suppressive needs with H_2RAs. Further studies are required to prospectively analyse the value of PPI withdrawal in patients with decompensated cirrhosis [31].

Acute interstitial nephritis (AIN)

The earliest published case of PPI-induced AIN was of a 74-year-old woman who had received 6 months of therapy with omeprazole and developed AIN with elevated serum creatinine, eosinophiluria and symptoms of malaise, fatigue and anorexia. The PPI was discontinued and the patient's symptoms resolved over 5 weeks. The patient was re-challenged with omeprazole and developed acute kidney injury and eosinophiluria after only two doses. The patient's symptoms resolved once the omeprazole was discontinued again. Omeprazole was implicated in 14 of the 15 cases. Fourteen of the 15 patients received a short course of corticosteroid therapy and 13 showed a rapid improvement in renal function. The onset of AIN is often insidious but withdrawal of the PPI can be sufficient to resolve the AIN. Patients should be counselled about the classic symptoms of AIN including nausea, vomiting, fatigue and hematuria and informed to seek medical attention when these symptoms persist.

PPI in elderly people

The use of PPIs is associated with an increased risk of all-cause death but not combined end-point outcome in older patients discharged from acute care units. The association between the use of PPIs and mortality remained significant after adjusting for well-known predictors of adverse outcomes in older populations, including age, cognitive impairment, disability, comorbidities, the use of drugs known to affect the prescription of PPIs, the number of drugs, and nutritional status. Recent findings show that PPI use is independently associated with all-cause mortality in 2 cohorts of institutionalized older people and in a group of patients discharged from acute care units. The results together with recent findings suggest that use of PPIs is associated with an excess mortality risk in older patients discharged from acute care units. Such findings need to be replicated using a randomized controlled design. In the meantime, physicians should balance benefits and harms in the long-term prescription of high-dose PPIs to older people with high comorbidity and polypharmacy and should periodically review the indications for PPI treatment to avoid unnecessary long-term prescriptions. Because hospitalization may not contribute to improving the appropriateness of PPI prescription [32].

Conclusions

The reported associations of PPI use and long term side effects have received considerable attention across a broad range of adverse effects. Clearly, the literature does show that some of these are related, albeit quite rare and more typically idiosyncratic (e.g. hypomagnesemia and interstitial nephritis). As such, these potential adverse effects should not be dismissed but put in perspective relative to the vast universe of patients receiving this class of therapy.

The evolving data on *C. difficile* should be monitored carefully. The clinical risk/benefit of any medical intervention or therapy always should be evaluated for each patient and appropriate use of therapy should be directed accordingly. Because PPIs are overprescribed in many patients, in particular for continued long-term use, the clinical effects always should be reviewed and attempts should be made to stop any therapy that may not be needed.

Conflict of interest

The author declares no conflict of interest

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