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EXPERT REVIEWS

Perils and pitfalls of long-term effects of proton pump inhibitors

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This review summarizes the literature regarding long-term adverse effects of proton pump inhibitors (PPIs). A PubMed search (1966 to February 2013) for English language studies was conducted using key terms PPI: omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprazole, rabeprazole, pneumonia, *Clostridium difficile*, osteoporosis, risk of fractures, thrombocytopenia, rhabdomyolysis, anemia, iron deficiency, hypomagnesemia, vitamin B_{12} and nephritis. The risk of pneumonia was increased 27–39% in short-term use of PPIs in three meta-analyses. *C. difficile* infections were also associated with the use of PPIs (odds ratio: 2.15; 95% CI: 1.81–2.55; $p < 0.00001$). This effect appears to be dose related. The US FDA has recently issued a warning regarding fractures and the impaired magnesium absorption associated with the use of PPI. Thrombocytopenia, iron deficiency, vitamin B_{12} deficiency, rhabdomyolysis and acute interstitial nephritis have also been reported with the use of PPIs. There is mounting evidence that PPIs are associated with serious adverse effects. Practitioners should be vigilant and counsel patients accordingly.

Keywords: anemia • *Clostridium difficile* • hypomagnesemia • nephritis • pneumonia • proton pump inhibitor • rhabdomyolysis • risk of fractures • thrombocytopenia • vitamin B_{12}

The secretion of gastric acid is a complex and continuous process incorporating neuronal, paracrine and endocrine pathways [1]. These separate signaling mechanisms converge at a common endpoint to promote the secretion of hydrogen ions by gastric parietal cells. 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 (Prilosec®, AstraZeneca, London, UK), lansoprazole (Prevacid®, Takeda Pharmaceuticals, Tokyo, Japan), pantoprazole (Protonix®, Wyeth Pharmaceuticals, NJ, USA), esomeprazole (Nexium®, AstraZeneca, London, UK), rabeprazole (AcipHex®, Eisai, Tokyo, Japan) and dexlansoprazole (Dexilant®, Takeda Pharmaceuticals). Despite their efficacy, long-term use of PPIs has been associated with several potential adverse effects including increased *Clostridium difficile* infections (CDI), risk of fractures and acute interstitial nephritis (AIN). With the prevalent use of PPIs and the availability of omeprazole and lansoprazole over-the-counter, the long-term use of PPIs and related safety issues are concerning [2–4].

Pharmacology of PPIs

Proton pumps are located on the plasma membrane of gastric parietal cells [1,5,6]. 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, about 24–48 h. PPIs are eliminated primarily via hepatic metabolism by cytochrome 2C19 and 3A4; renal elimination is negligible.

Overuse of PPIs

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 [7]. The efficacy, availability

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and ease of use of PPIs has led to overuse in both outpatient and inpatient settings [8–11]. 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 such as pneumonia, *C. difficile* diarrhea, risk of fractures, hypomagnesemia, thrombocytopenia, iron deficiency, vitamin B_{12} deficiency, rhabdomyolysis, AIN, enteric infections and neoplasms. This review will address some the major adverse reactions associated with long-term PPI use that have resulted in labeling changes or have recently been discussed in the literature.

Materials & methods

A search of PubMed from 1966 to February 2013 was conducted using the following key terms: PPI, omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprazole, rabeprazole, pneumonia, *C. difficile*, osteoporosis, risk of fractures, thrombocytopenia, rhabdomyolysis, anemia, iron deficiency, hypomagnesemia, vitamin B_{12} and nephritis. Studies included for this review were limited to English language. Bibliographies of recent review articles and systematic reviews were hand searched to identify any additional studies. Studies and case reports were not included if there were confounding variables in addition to PPI use that could explain the adverse effect in question.

Results

Pneumonia

Aerobic bacteria grow in the stomach as the intragastric pH increases due to PPIs [12]. Bacterial presence in the gastric content may lead to microaspiration and lung colonization with a potential of causing pneumonia [13]. There are three meta-analyses of published case–control and cohort trials that show an increased risk of pneumonia with the use of PPIs [14–16]. Two of the meta-analyses focus on community-acquired pneumonia (CAP) while the third one includes both community- and hospital-acquired pneumonia. The overall risk of CAP is shown to be: odds ratio (OR): 1.36 (95% CI: 1.12–1.65) [15] and 1.39 (95% CI: 1.09–1.76) [14]. Giuliano *et al*. also showed that high-dose PPI (OR: 1.50; 95% CI: 1.33–1.68) and low-dose PPI (OR: 1.17; 95% CI: 1.11–1.24) were significantly associated with CAP [14]. Short-term use of PPI (<30 days) was also significantly associated with pneumonia (OR: 1.65; 95% CI: 1.25–2.19) [14]. Chronic use of PPIs (>180 days) was not associated with CAP (OR: 1.10; 95% CI: 1.00–1.21) [14]. The third meta-analysis combines both CAP and hospital-acquired pneumonia and shows that the risk of pneumonia is increased with PPI use (OR: 1.27; 95% CI: 1.11–1.46) [16]. A recent nested case–control study showed an increased risk of community-acquired pneumonia in patients currently receiving PPIs (adjusted OR [aOR]: 1.29; 95% CI: 1.15–1.45) [17]. It was also noted that more than one dose of PPI per day and short-term (1–15 days) use was associated with increased risk of pneumonia (aOR: 1.33, 95% CI: 1.06–1.65, p = 0.012; aOR: 1.25, 95% CI: 0.91–1.71, p < 0.05, respectively). There is also some evidence that PPIs may be associated with pneumonias in children [18]. Only those patients with an appropriate indication should be initiated on PPIs and doses should be optimized for indications.

C. difficile

CDI are on the rise. As well, infections due to a more virulent strain North American Pulse-field type 1 strain are becoming more common [19]. At normal gastric pHs, most enteric bacteria are inhibited [20]. PPIs increase gastric pH, which allows bacteria including *C. difficile* to survive and proliferate in this environment. In a meta-analysis of 30 trials of 202,965 patients, CDI was significantly greater in patients who had received PPI therapy (OR: 2.15; 95% CI: 1.81–2.55; p < 0.00001) [21]. Since antibiotic use is associated with CDI, a subgroup analysis was performed. Regardless of antibiotic use, PPIs were still associated with CDI in subgroup analyses based on percent of subjects within each trial who used antibiotics (antibiotic use >80% OR: 2.07; 95% CI: 1.5–2.86; antibiotic use ≤80% OR: 2.73; 95% CI: 1.88–3.97). In a pharmacoepidemiological cohort study of 101,796 patients over a 5-year period, CDI also increased with the degree of acid suppression [22]. Compared with patients who did not receive acid suppressive therapy, the risk of CDI was higher in patients taking a histamine-2 receptor antagonist, a daily PPI or a PPI dose greater than daily (OR: 1.53; 95% CI: 1.12–2.10; OR: 1.74, 95% CI: 1.39–2.18; OR: 2.36; 95% CI: 1.79–3.11, respectively). Owing to the widespread use and over-the-counter availability of PPI, patients need to be counseled regarding the risk of CDI.

Risk of fractures

Calcium is normally ingested as either calcium carbonate or calcium chloride [23,24]. These calcium salts are poorly soluble and require an acidic environment to increase the ionization of calcium. 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. Elevated levels of parathyroid hormone increase the rate of osteoclastic bone resorption. Over time, this can lead to a reduction in bone mass, ultimately increasing the risk of bone fractures. A randomized, double-blind, placebo-controlled, crossover trial of 18 patients demonstrated that 7 days of omeprazole therapy use can significantly decrease calcium absorption from 9.1 to 3.5% (p = 0.003) under fasting conditions in elderly women [25]. These results are supported by a retrospective cohort study that found an association between the prescribing of antiosteoporosis medication following the prescribing of PPIs compared with those not receiving a PPI (OR: 1.69; 95% CI: 1.66–1.72) [26]. It was more likely for patients to receive antiosteoporosis medications the longer PPI therapy was continued. Patients who received PPIs for 6–12 months and for >24 months were more likely to receive antiosteoporosis medications compared to patients who received PPIs for less than 3 months (OR: 1.19, 95% CI: 1.15–1.23 and OR: 2.09, 95% CI: 2.04–2.13, respectively).

There are several epidemiological studies evaluating the association of PPI use and fracture risk [27–34]. The majority of these studies show an association of PPI use and the development of fractures. Table 1 summarizes the findings of these studies. Overall fracture risk was increased with the use of PPIs [27,29,33]. The risk of fractures increased with longer duration of PPIs [29].

Table 1. Epidemiological studies of fracture risk with proton pump inhibitors use.

Study (year)	Study population	Overall fracture risk	Risk of hip fracture	Other fractures	Ref.
Retrospective					
Vestergaard *et al.* (2006)	124,655 cases with fractures 373,962 matched controls No age range specified PPI use within the last year	OR: 1.18 (95% CI: 1.12–1.43)	OR: 1.45 (95% CI: 1.28–1.65)	Risk of spine fracture; OR: 1.60 (95% CI: 1.25–2.04) Risk of forearm fracture; OR: 0.95 (95% CI: 0.82–1.11)	[27]
Yang *et al.* (2006)	13,556 cases with fractures 135,386 matched controls Age ≥50 years		PPI use >1 year; aOR: 1.44 (95% CI: 1.30–1.59) High-dose (>1.75 doses/day) PPI use >1 year: aOR: 2.65 (95% CI: 1.80–3.90) PPI use: 1 year; aOR: 1.22 (95% CI: 1.15–1.30) PPI use: 4 years; aOR: 1.59 (95% CI: 1.39–1.80)		[28]
Targownik *et al.* (2008)	15,792 cases with fractures 47,289 matched controls Age ≥50 years	PPI use ≥7 years; aOR: 1.92 (95% CI: 1.16–3.18)	PPI use ≥5 years; aOR: 1.62 (95% CI: 1.02–2.58) PPI use ≥6 years; aOR: 2.49 (95% CI: 1.33–4.67) PPI use ≥7 years; aOR: 4.55 (95% CI: 1.68–12.29)		[29]
Kaye & Jick (2008)	1098 cases with fractures 10,923 matched controls Age: 50–70 years		RR: 0.9 (95% CI: 0.7–1.11)		[30]
Corley *et al.* (2010)	33,752 cases with fractures 130,471 matched controls Age ≥18 years		≥2 years of PPI use and one other risk factor; OR: 1.30 (95% CI: 1.21–1.39) PPI dose >1.5 pills/day: OR: 1.41 (95% CI: 1.21–1.64)		[31]
Prospective					
Yu *et al.* (2008)	Women (4574 non-PPI users and 234 PPI users) Men (4920 non-PPI users and 487 PPI users) Age ≥65 years		Women: aRH: 1.16 (95% CI: 0.80–1.67) Men: aRH: 0.62 (95% CI: 0.26–1.44)	Risk of nonspine fracture Women: aRH: 1.34 (95% CI: 1.10–1.64) Men: aRH: 1.21 (95% CI: 0.91–1.62)	[32]
Gray *et al.* (2010)	2831 PPIs users 127,756 non-PPIs users Postmenopausal women Age: 50–79 years	aHR: 1.25 (95% CI: 1.15–1.36)	aHR: 1.00 (95% CI: 0.71–1.40)	Risk of spine fracture; aHR: 1.47 (95% CI: 1.18–1.82) Risk of wrist fracture; aHR: 1.26 (95% CI: 1.05–1.51)	[33]
Khalili *et al.* (2012)	79,899 postmenopausal women Mean age: 67 years		aHR: 1.36 (95% CI: 1.13–1.63) aHR at 2 years: 1.36 (95% CI: 1.12–1.65) aHR at 4 years: 1.42 (95% CI: 1.05–1.93) aHR at 6–8 years: 1.54 (95% CI: 1.03–2.31) aHR nonsmoking: 1.06 (95% CI: 0.77–1.46) aHR smoking: 1.51 (95% CI: 1.20–1.91)		[34]

aHR: Adjusted hazard ratio; aOP: Adjusted odds ratio; aRH: Adjusted relative hazard; OR: Odds ratio; PPI: proton pump inhibitor; RR: Relative risk.

Five studies [27–29,31,34] showed a significant increase in hip fractures, while three studies [30,32,33] did not. In one case–control study of patients with and without hip fractures, PPIs were associated with an increased risk of hip fracture particularly in patients who had at least one other risk factor for fracture, including: alcohol abuse, arthritis, diabetes mellitus, kidney disease or glucocorticoid use [31]. In another study, smoking was significantly associated with increased risk of hip fractures in PPI users [34]. The risk of hip fracture increased significantly with longer duration of PPI use [29,34]; however, this was not consistently seen [31]. Similarly, high-dose PPI therapy defined as greater than 1.5 doses per day was associated with a significantly higher risk of hip fracture [28,31]. Risk of spine fracture was significantly higher with PPI use [27,33], whereas the risk of developing nonspine fractures was only significantly higher in women [32]. Wrist fracture but not forearm fracture risk was significantly higher with PPI use [27,33].

The epidemiological studies are large based on the databases used; however, they are retrospective in nature. A prospective trial of 1211 postmenopausal women offers additional evidence that PPI use is an independent risk factor for vertebral fractures [35]. Risk of vertebral fractures was significantly higher for omeprazole users compared with nonusers (relative risk [RR]: 3.41; 95% CI: 1.45–8.01; p = 0.005). This relationship was maintained in a multivariate analysis, omeprazole use was an independent predictor of vertebral fractures (RR = 3.10; 95% CI: 1.14–8.44; p = 0.027). Several meta-analyses have found an association between PPIs and the development of fractures [36–39].

Recently, the US FDA issued a warning regarding PPI use and the risk of developing fractures [40]. 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.

Hypomagnesemia

There are several case reports and case series in the literature documenting an association between PPIs and hypomagnesemia [41–52]. 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 rechallenge, hypomagnesemia developed within a couple of weeks of reinitiation of PPI therapy. In some of the cases reported, patients presented with clinical manifestations of hypomagnesemia including seizures, cardiac events and tremors. In a retrospective cross-sectional study of 487 patients admitted to a rural community institution, 207 were PPI users and 280 were nonusers [53]. 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 (aOR: 2.5; 95% CI: 1.43–4.36). The FDA includes a warning regarding PPI use and the risk of hypomagnesemia [54]. Patients may be at higher risk of developing hypomagnesemia and related clinical manifestations that may be related to the duration of PPI therapy.

Thrombocytopenia

There is very little published about the association between PPIs and thrombocytopenia. In a case report, a patient receiving lansoprazole 60-mg twice daily to treat a GI bleed experienced a platelet decline from $160 \times 10^3/mm^3$ to $36 \times 10^3/mm^3$ over a 3-day period [55]. After lansoprazole was discontinued and ranitidine started, the platelet count rebounded to $105 \times 10^3/mm^3$ at discharge and eventually increased to $215 \times 10^3/mm^3$. The authors reported a possible association between thrombocytopenia and lansoprazole. There is a report of two cases involving the use of pantoprazole and thrombocytopenia [56]. In the first case, pantoprazole was started for GI prophylaxis in 62-year-old female with a history of sickle cell disease and cerebrovascular accident. Upon admission, her platelets were $340 \times 10^3/mm^3$ and fell to $87 \times 10^3/mm^3$ over a 6-day period. In the second case, a 42-year-old man with short gut syndrome who was receiving lansoprazole at home was initiated on pantoprazole upon admission to the hospital. His platelets fell from $244 \times 10^3/mm^3$ to $75 \times 10^3/mm^3$ over a 5-day period. In both cases, the hemoglobin remained stable and none of the other medications concurrently administered were associated with thrombocytopenia. According to the authors, there was a probable association between PPIs and the thrombocytopenia based on the Naranjo score. In another case, an infant experienced thrombocytopenia after initiation of pantoprazole for GI prophylaxis [57]. However, the patient's medical course was complicated by sepsis and disseminated intravascular coagulation. Heparin and milrinone were also used during treatment. The Naranjo probability scale indicates a possible relationship between pantoprazole and thrombocytopenia in this infant but a definite cause cannot be established. 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 (6.2%, 95% CI: 4.1–8.7%; 6.6%, 95% CI: 4.5–9.2%, respectively, p = 0.90) [58]. The long-term use of PPIs and thrombocytopenia cannot be firmly established and it is unclear whether routine monitoring of platelet count is necessary.

Iron deficiency

Iron absorption depends on both the specific type of iron and the pH of the gastric lumen. Heme-type iron comprises approximately 30% of the iron in a normal Western diet and is readily absorbed from the GI tract independent of gastric pH [59,60]. Non-heme iron constitutes approximately 70% of ingested iron and requires an acidic environment for absorption. When the gastric pH is less than 3, ferric ions are reduced to ferrous ions, which are 100 times more soluble in the intestinal lumen [61,62]. If the gastric lumen remains at a pH greater than 3, ferric ions are poorly reduced to ferrous ions, therefore, decreasing absorption. Radiolabeled iron absorption tests in healthy human volunteers using antacids demonstrated a 52% decrease in iron absorption

whereas volunteers using cimetidine had a 28% decrease in iron absorption [63]. Since PPIs are the most potent inhibitors of gastric acid secretion compared with antacids or histamine$_2$-receptor antagonists, it is possible that iron absorption may be impaired [64]. Case reports have suggested an association between PPIs and iron deficiency. A 49-year-old male receiving omeprazole 40 mg daily developed iron deficiency anemia after 3 years with initial serum iron level of 34 mcg/dl (normal range: 47–153 mcg/dl) [64]. Upon discontinuation of omeprazole, the anemia improved and serum iron level normalized to 133 mcg/dl. A similar case of a 51-year-old female receiving omeprazole 20 mg daily for 6 months developed iron deficiency anemia with a hemoglobin concentration of 9.9 g/dl, which improved after discontinuation of the drug to 11.5 g/dl [65]. In a study of 34 patients who were receiving continuous omeprazole treatment for 6–48 months, three patients demonstrated serum ferritin levels below the lower limit of normal and two patients demonstrated low serum iron levels [66]. However, the low serum iron in these patients may be due to underlying conditions of Hodgkins lymphoma or Type 2 diabetes mellitus with active scleroderma. Another study assessed 14 patients with hereditary hemochromatosis. These patients received a meal high in non-heme iron before and after 7 days of either omeprazole or lansoprazole. Peak serum iron concentrations were significantly lower after treatment with PPI (13.6 vs 6.1 mmol/l; $p < 0.01$) [67]. PPI-induced iron deficiency has yet to be firmly established and routine serum iron monitoring may not be indicated.

Vitamin B_{12} deficiency

Cobalamin is a water soluble vitamin that is tightly bound to dietary protein [68]. In the gastric mucosa, hydrochloric acid and pepsin act to release cobalamin from dietary proteins, allowing it to bind to salivary R proteins, which act to transfer cobalamin to intrinsic factor. The cobalamin–intrinsic factor complex remains intact until it reaches the distal ileum where the cobalamin is absorbed. Protein bound cobalamin may not be adequately released from food in the presence of achlorhydria secondary to PPI therapy. In a double-blind, crossover study, 17 healthy males were given a single dose of either omeprazole 80 mg intravenously (iv.) or placebo to determine the extent of cobalamin absorption [69]. PPI did not significantly impair cobalamin absorption. In another study, ten healthy male volunteers were assigned to oral omeprazole 20 mg daily or omeprazole 40 mg daily for 2 weeks [70]. Cobalamin absorption after 2 weeks was compared with their respective baseline values. In the 20- and 40-mg groups, cobalamin absorption decreased from 3.2–0.9% ($p = 0.031$) and 3.4–0.4% ($p = 0.05$), respectively. A major limitation to this study is that no placebo was used and, therefore, it is not possible to determine if decreased cobalamin plasma levels were due to actual cobalamin malabsorption or failure of cobalamin liberation from food [71]. Two studies analyzed vitamin B_{12} levels in patients with Zollinger–Ellison syndrome who were treated with PPIs [72,73]. In the first study, 111 patients who received omeprazole had significantly lower vitamin B_{12} levels compared with 20 patients who received histamine-2 receptor antagonists (459 ± 225 pg/ml vs 582 ± 285 pg/ml, respectively, $p = 0.04$) [72]. In the second study, six of 61 patients receiving PPIs were found to have low vitamin B_{12} levels however, no clinical manifestations of vitamin B_{12} deficiency were noted after an average of 8 years or more of PPI therapy [73]. In a retrospective analysis of 36 patients, 17 patients received PPI for at least 12 months and 19 served as controls [74]. Seventy five percent of patients receiving PPI and 11% of control group patients were vitamin B_{12} deficient ($p = 0.006$). In a retrospective trial of 113 pediatric patients, 87 had vitamin B_{12} levels assessed. All 87 patients had a normal vitamin B_{12} level after being treated with a PPI for a median of 35 months [75]. In a trial of 125 long-term (>3 years) PPI users older than 65 years of age, no association was found between long-term PPI use and vitamin B_{12} status ($p = 0.73$) [76]. It may be appropriate to obtain baseline cobalamin levels and monitor these levels during long-term PPI therapy.

Rhabdomyolysis

The most common causes of rhabdomyolysis include traumatic injury or excessive muscle activity. PPIs are a less common cause of rhabdomyolysis [77]. In a case report, a patient with ulcerative esophagitis was treated with pantoprazole and developed rhabdomyolysis after 2 days of treatment [78]. However, the patient had several comorbid conditions and was also being treated with NSAIDS, which have been associated with rhabdomyolysis [79]. In another case report, a 56-year-old Japanese male admitted with history of alcohol use and hematemesis due to Mallory–Weiss syndrome developed rhabdomyolysis after 5 days of treatment with omeprazole 20 mg iv. twice daily [80]. The diagnosis of rhabdomyolysis was based on laboratory parameters, and the patient did not demonstrate any physical signs or symptoms. Most recently, a 75-year-old male being treated with esomeprazole for stress ulcer prophylaxis while hospitalized in the intensive care unit following cardiac bypass surgery experienced continually increasing myoglobin until esomeprazole was discontinued [81]. One day after cessation of esomeprazole, the myoglobin decreased until it remained persistently stable and within normal limits. 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 [82]. 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.

Acute interstitial nephritis

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 and eosinophiluria and symptoms of malaise, fatigue and anorexia [83]. The PPI was discontinued and the patient's symptoms resolved over 5 weeks. The patient was rechallenged with omeprazole and developed acute kidney injury and eosinophiluria after only two doses. The patient's symptoms resolved once the omeprazole was discontinued again. Similar findings were documented in other case reports [84–91]. The onset of AIN was between 10 days and 18 months after PPI initiation in 15 cases [92]. 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. In a study of seven cases, the onset of AIN due to PPI ranged from 1 day to 4 months [12]. Six of the seven patients spontaneously recovered after discontinuation of PPI and one required corticosteroids for recovery of renal function. One patient was rechallenged and developed AIN within 12 h of receiving the PPI. Similar results were found in two retrospective analyses and a systematic review [93–95]. The onset of AIN is often insidious but withdrawal of the PPI can be sufficient to resolve the AIN. Patients should be counseled about the classic symptoms of AIN including nausea, vomiting, fatigue and hematuria and informed to seek medical attention when these symptoms persist.

Expert commentary

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 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 AIN have also been reported with the use of PPIs.

There are some limitations to the data in this review. Many of the adverse effects are relatively rare and are reported as cases and case series. In other literature, adverse effects are reported in cohort and case–control studies based on retrospective databases. Some of the studies adjusted for potential confounding factors are known to increase the risk of a particular adverse effect, while others do not. For example, in the studies assessing the risk of pneumonia, many trials adjust for risk factors of pneumonia such as alcohol use, underlying GERD and chronic obstructive pulmonary disease; however, the risk factors used varied from study to study. In addition, the risk of developing pneumonia with short-term PPI use may be attributed to a protopathic bias, wherein early signs of pneumonia may have been mistreated as GERD with PPIs. In the case of hip fracture risk, study results are conflicting. This may be secondary to the retrospective nature of the studies and using information from databases which may result in missing or incorrectly coded data. Missing data may not allow for adjustment for other confounding risk factors for fractures such as smoking history, alcohol intake, age, family history, height and weight, history of immobility, dizziness or falls and timing of PPI use in relation to worsening osteoporosis. The nature of the data used also makes it difficult to assess adherence to PPI therapy. Several reports discuss laboratory-based adverse effects (i.e., magnesium level, platelet count, B_{12} concentration) but do not relate these to clinical manifestations, which makes it difficult to determine the clinical significance of these effects. The published meta-analyses are based on small or retrospective studies and include heterogeneous patient populations with varied indications, duration and doses of PPIs. Most trials combined the different PPIs to assess adverse effects. Based on the available data, it is difficult to determine whether these adverse effects are due to a class effect of all PPIs or are specific to a particular PPI.

Although PPIs are most commonly associated with minor adverse effects such as headache, nausea, abdominal pain, flatulence and diarrhea, there is mounting evidence that they are associated with more serious adverse events. Practitioners need to be vigilant about such adverse effects and counsel patients accordingly and use PPIs only when indicated.

Five-year view

There is sufficient literature questioning the safety of PPIs. The clinician and the public need to be educated regarding appropriate and safe use of PPIs, given the widespread use of these agents. Clinicians need to use PPIs more judiciously and use minimum duration and dose for a given indication. Professional societies need to update clinical recommendations to incorporate and balance potential PPI toxicities with appropriate use to guide clinicians. In addition, there is a need for continued surveillance of these agents particularly for adverse effects that are less frequently documented in the literature. As well, several theories exist with respect to the mechanism of these adverse effects, however, these need to be further elucidated.

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. This is partly due to the availability of PPIs over-the-counter. Patients may self treat for an indefinite duration for questionable indications without knowing the potential serious adverse effects of these agents. It may be beneficial to make PPIs available behind the counter. This will allow pharmacists to evaluate their use and have a discussion regarding the benefits and risks of these agents with their patients.

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Key issues

- There is mounting evidence that proton pump inhibitors (PPIs) are associated with serious adverse effects.
- The risk of pneumonia is increased in short-term use of PPIs.
- *Clostridium difficile* infections are associated with the use of PPIs in a dose-related fashion.
- PPIs now have a US FDA warning regarding fractures and impaired magnesium absorption.
- Thrombocytopenia, iron deficiency, vitamin B_{12} deficiency, rhabdomyolysis and acute interstitial nephritis have also been reported with the use of PPIs.
- Practitioners should be vigilant and counsel patients accordingly.

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