

Long-term Safety Concerns with Proton Pump Inhibitors

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ABSTRACT

Proton pump inhibitors (PPIs) are among the most widely prescribed medications worldwide. Their use has resulted in dramatic improvements in treatment of peptic ulcer disease and gastroesophageal reflux disease. Despite an acceptable safety profile, mounting data demonstrate concerns about the long-term use of PPIs. To provide a comprehensive review regarding the concerns of long-term PPI use, a literature search was performed to identify pertinent original and review articles. Despite study shortcomings, the collective body of information overwhelmingly suggests an increased risk of infectious complications and nutritional deficiencies. Data regarding any increased risk in gastric or colon malignancy are less convincing. PPIs have revolutionized the management and complications of acid-related disorders with a high margin of safety; however, with the data available, efforts to reduce the dosing of or discontinue the use of PPIs must be reassessed frequently.

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Proton pump inhibitors (PPIs) are the most potent medications available to reduce gastric acid secretion. Since their introduction in the late 1980s, these efficacious acid suppressants have rapidly assumed a major role for the treatment of acid-peptic disorders. They are now among the most widely prescribed drugs worldwide because of their outstanding efficacy and safety. In 2006, expenditure on these drugs was estimated to be approximately \$24 billion globally.¹ Although these drugs are considered safe and have been approved for long-term use, some long-term safety concerns have been raised.² In recent years, potential adverse effects, such as increased risk of respiratory infections, *Clostridium difficile* infection, and, most recently, bone fractures, have been identified with long-term PPI use. With the widespread use of PPIs, the potential long-term safety issues that have been described in recent years mandate review.

PHARMACOLOGY OF PROTON PUMP INHIBITORS

PPIs are substituted benzimidazole derivatives that inhibit the proton pump (H⁺/K⁺ adenosine triphosphatase) in the

parietal cells of the stomach. PPIs work by accumulating in the secretory canaliculus of the acid-secreting parietal cell, where they are protonated to the active form, a cationic sulfonamide. This active form then binds to a sulfhydryl group on the proton pump and, by irreversible inhibition, prevents secretion of acid into the gastric lumen. Acid secretion resumes only after new pump molecules are synthesized, providing a prolonged (24-48 hours) suppression of acid secretion. PPIs undergo rapid first-pass and systemic hepatic metabolism by hepatic cytochrome P, particularly cytochrome P2C19 and cytochrome P3A4, and have negligible renal clearance.³ PPIs are used for many medical conditions. Table 1 presents a list of clinical conditions for which PPIs are currently being used.

OVERUSE OF PROTON PUMP INHIBITORS

A major concern about PPIs is their potential overuse and abuse. Several studies have confirmed the overuse of these agents in both inpatient and outpatient settings. Approximately 50% to 60% of prescriptions of acid-suppressive medications in hospitalized patients are found to be without appropriate indications.⁴⁻⁶

SIDE EFFECTS OF PROTON PUMP INHIBITORS

PPIs generally cause few adverse effects. The most common side effects are headaches, nausea, abdominal pain, constipation, flatulence, and diarrhea. These side effects are usu-

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ally mild, self-limiting, and unrelated to dosage or age. However, long-term side effects of PPIs have recently gained attention, and several studies have looked at various side effects that may be associated with potential long-term use of PPI. These side effects are discussed in detail.

Vitamin B₁₂ Deficiency

Vitamin B₁₂ is normally ingested in a protein-bound state. Gastric acid is necessary for releasing it from this bound state to bind to the R protein. In the duodenum, the vitamin is split from the R protein by the action of pancreatic enzymes, bound to intrinsic factor, and absorbed in the small intestine.⁷

It has been known for many years that the absorption of protein-bound vitamin B₁₂ is decreased during H₂ blocker treatment.⁸ Initial results with omeprazole failed to show this effect;⁹ however, subsequent studies showed decreased vitamin B₁₂ absorption with PPI administration. In one study, cyanocobalamin absorption decreased from 3.2% to 0.9% ($P = .031$) in participants receiving 20 mg of omeprazole daily, and the effect was even more pronounced with higher dose.¹⁰ In a study of 131 patients treated with either omeprazole ($n = 111$) or histamine H₂-receptor antagonists ($n = 20$), serum vitamin B₁₂ and folate levels were measured. The mean duration of omeprazole treatment was 4.5 years. Vitamin B₁₂ levels, but not serum folate levels, were significantly ($P = .03$) lower in patients treated with omeprazole.¹¹ Similarly, the association of B₁₂ deficiency with PPI use in elderly patients is supported by many case reports published in the last decade. However, a recent case-control study investigated 125 long-term (>3 years) PPI users aged 65 years or more. No differences in mean vitamin B₁₂ levels were observed between the long-term PPI users and their partners ($P = .73$). Regular screening of vitamin B₁₂ levels in elderly patients receiving long-term treatment with PPIs was therefore not recommended by the authors.¹² More recently,

methylmalonic acid and homocysteine levels have been used to assess subclinical changes in cyanocobalamin (vitamin B₁₂) preceding a decrease in serum B₁₂ levels. Thirty-one percent of patients receiving long-term therapy with PPI were found to have evidence of subclinical B₁₂ deficiency.¹³ Vitamin B₁₂

deficiency with acid suppression is intriguing. Studies have produced mixed results. Most case series and case-control studies have supported the association of vitamin B₁₂ deficiency with PPIs, whereas some have failed to establish the association. Studies showing the effects of acid inhibition on B₁₂ absorption are listed in Table 2 for review.

Current evidence of B₁₂ deficiency associated with long-term PPI use is based on small nonrandomized retrospective studies. Until large prospective randomized studies are conducted, the association of PPI use with B₁₂ deficiency cannot be firmly established, and routine monitoring of B₁₂ levels is not indicated.

Iron Deficiency

Dietary iron is present in food as either non-heme iron or heme

iron. Dietary non-heme iron absorption is markedly improved in the presence of gastric acid.¹⁴ Several clinical studies suggest that gastric acid hyposecretion, especially over a prolonged period, might result in clinically significant malabsorption of iron. Decreased non-heme iron absorption has been reported in patients with achlorhydria¹⁵ and various gastric acid-hyposecretory conditions (gastric resection, vagotomy, atrophic gastritis).⁷ To assess iron stores and the occurrence of iron-deficiency anemia in patients with Zollinger-Ellison syndrome treated long-term with gastric antisecretory drugs, Stewart et al¹⁶ studied 109 patients with Zollinger-Ellison syndrome. Continuous treatment with omeprazole for 6 years or continuous treatment with any gastric antisecretory drug for 10 years did not cause decreased body iron stores or iron deficiency. These results suggest that iron deficiency secondary to decreased gastric acid secretion is theoretically possible but has not been clinically proven; thus, monitoring for iron deficiency is not necessary.

However, it must be noted that Zollinger-Ellison syndrome is a rare disorder, and the results cannot be applied to the average PPI user. In the absence of such data, the results of such studies cannot be applied to the general population, and there is a need for long-term safety data trials in the average patient population using PPIs for more general indications, such as reflux disease.

CLINICAL SIGNIFICANCE

- Proton pump inhibitors (PPIs) are the most potent medications available to reduce gastric acid secretion.
- With the widespread use of PPIs, the long-term safety issues need to be considered.
- The collective body of information overwhelmingly suggests increased risk of infectious complications and nutritional deficiencies.
- Data on the risk of increased gastric and colon malignancy, despite a physiologic theoretic basis, are less convincing.
- The long-term need for PPIs must be reassessed frequently.

Table 1 Common Clinical Uses of Proton Pump Inhibitors

Clinical Uses of Proton Pump Inhibitors

Gastroesophageal reflux disease
 Peptic ulcer disease
Helicobacter pylori eradication
 Risk reduction of NSAID-associated gastric ulcer
 Non-ulcer dyspepsia
 Zollinger-Ellison syndrome

NSAID = nonsteroidal anti-inflammatory drug.

Table 2 Studies Performed to Evaluate the B₁₂ Deficiency with Acid Inhibition

Author	Study Design	Drug Used	No. of Patients	Duration of Study	Results
Steinberg et al ⁸	Case control	Cimetidine	12	Unknown	Reversible malabsorption of protein-bound cobalamin
Koop and Bachem ⁹	Case series	Omeprazole	34	2 y	No change in B ₁₂ levels
Marcuard et al ¹⁰	Case series	Omeprazole	10	2 wk	Decrease cyanocobalamin absorption in dose-dependent manner
Termanini et al ¹¹	Case series	Omeprazole/ranitidine	131	4.5 y PPI 10 y H2 blockers	Duration of omeprazole treatment inversely correlated with B ₁₂ levels
den Elzen et al ¹²	Case control	PPIs	125	>3 y	No association found
Hirschowitz et al ¹³	Case series	Lansoprazole	61	Up to 18 y	10% loss in B ₁₂ level, 31% subclinical decrease by MMA and HC

MMA = methylmalonic acid; HC = homocysteine; PPI = proton pump inhibitor.

Calcium Deficiency and Risk of Osteoporosis

Calcium solubility is thought to be important for its absorption.¹⁷ An acidic environment in the gastrointestinal tract facilitates the release of ionized calcium from insoluble calcium salts.¹⁸ In vitro, calcium carbonate disintegration and dissolution are pH dependent. As pH increases, disintegration and dissolution slow, decreasing from 96% at a pH of 1 to 23% at a pH 6.1.¹⁹ Significant hypochlorhydria, particularly among the elderly population, could theoretically result in calcium malabsorption. Animal and human studies have shown that PPI therapy might decrease insoluble calcium absorption or bone density.²⁰ Alternatively, limited in vitro and human data also suggest PPIs might decrease bone resorption by inhibiting osteoclastic vacuolar H⁺-K⁺-adenosine triphosphatase.^{21,22} Several clinical studies have attempted to examine the outcome of these conflicting effects. A randomized, double-blind, placebo-controlled, crossover clinical trial was conducted in women aged more than 65 years and found that a 1-week course of 20 mg omeprazole per day significantly decreased fractional calcium absorption.²³ In another large case-control study of the Danish population, PPIs were found to be associated with an increased fracture risk for use within the last year (odds ratio [OR] 1.45 for hip fracture) compared with H2 blockers (OR 0.69).²⁴ Another well-conducted case-control study also demonstrated an increased risk of hip fracture among patients prescribed PPI for more than 1 year, especially among those prescribed greater than once-daily dosing. The adjusted OR was 1.44 for hip fracture associated with more than 1 year of PPI therapy. The risk of hip fracture was significantly increased among patients prescribed long-term high-dose PPIs (adjusted OR, 2.65; $P < .001$).²⁵

There is not enough evidence to suggest all patients receiving long-term PPI therapy be screened for osteoporosis. The studies supporting the association of PPI with calcium deficiency are limited by their retrospective designs,^{24,25} and the only prospectively conducted trial is limited by a short duration of only 1 week;²³ thus, the long-term effects of PPI cannot be interpreted. On the basis

of the current evidence, screening for osteoporosis cannot be recommended for patients using PPIs for the long-term. Because the prevalence of both acid-related gastrointestinal disorders and osteoporosis is increasing, a clearer understanding of the effects of PPIs on calcium metabolism is, however, urgently required.

Risk of Infections

Gastric acidity constitutes a major defense mechanism against ingested pathogens, and loss of the normal stomach acidity has been associated with colonization of the normally sterile upper gastrointestinal tract.²⁶ Acid-suppressive agents such as PPIs and H2-receptor antagonists increase gastric pH, and PPIs also have been shown to affect leukocyte function.²⁷ These factors contribute to the reported associations with an increased risk of respiratory tract²⁸ and enteric infections, including hospital and nursing home-acquired *C. difficile*-associated diarrhea.^{29,30}

Clostridium difficile Infection

Recent data suggest that both the rate and the severity of nosocomial *C. difficile*-associated diarrhea are increasing.³¹ The hypothesis that reduction in gastric acid might be relevant to *C. difficile* acquisition is biologically plausible, because even though the spores are relatively resistant to acid, vegetative cells are highly susceptible.³² Because the major mode of transmission of *C. difficile* is believed to be via spores, which are acid resistant, the biological plausibility of an elevated risk of *C. difficile*-associated diarrhea with gastric acid-suppressive agents has been questioned. It has been demonstrated in a hamster model that 75% of ingested spores transformed into the vegetative state within 1 hour of ingestion,³² at which time they were located in the small intestine. It is possible that, in humans, if conversion of *C. difficile* to the vegetative phase is occurring while the spores are still in the stomach, their survival may be facilitated by elevated gastric pH levels. Other mechanisms also are possible, such as gastrin-mediated direct effects on colonic mucosa³³ and effects on immune function.²⁷ Earlier

Table 3 Studies Performed to Evaluate the Risk of Enteric Infections with Acid Suppression

Author	Study Design	Patient No.	Infection Type	Results
Neal et al ⁴²	Case-control	188	Salmonella	RR of 2.4 with H ₂ blockers
Neal et al ⁴³	Case-control	211	Campylobacter	RR of 10.5 with use of PPI
Neal ⁶⁸	Case-control	531	Campylobacter	RR of 3.4 with use of PPI
Doorduyn ⁶⁹	Case-control	573	Salmonella	RR of 4.2 with use of PPI <i>Salmonella enteritidis</i> RR of 11.2 with <i>S. typhimurium</i> DT104
Leonard et al ³⁹	Meta-analysis	11,280	Enteric infections	RR of 3.3 with use of PPI

RR = relative risk; PPI = proton pump inhibitor.

studies revealed poor association of *C. difficile* infection with acid suppression. In their retrospective data of 126 patients, Shah et al³⁴ found an increased association only with antibiotics ($P = .0004$), tube feeding ($P < .0005$), and hypoalbuminemia ($P = .01$).³⁴ Similarly, another study found an OR of 0.92 with the use of PPIs and risk of *C. difficile* infection.³⁵ Recent studies have suggested an association with *C. difficile* and PPI therapy. Hypochlorhydria is more common in the elderly³⁶ and may contribute to the high incidence of *C. difficile* in this patient group. Bypassing the gastric acid barrier also would be consistent with the findings that post-pyloric tube feeding was associated with *C. difficile* diarrhea with an OR of 11.4 (95% confidence interval [CI], 1.3-103.7), whereas pre-pyloric tube feeding had an OR of 3.5 (95% CI, 0.19-66.5).³⁷ In a large population-based case-control study, the adjusted OR of *C. difficile*-associated diarrhea was found to be 2.9 with current use of PPIs.³⁸ A recent systematic review concluded an increased risk of taking antisecretory therapy in those infected with *C. difficile* (pooled OR 1.94; 95% CI, 1.37-2.75). The association was greater for PPI use (OR 1.96; 95% CI, 1.28-3.00) compared with H₂-receptor antagonist use (OR 1.40; 95% CI, 0.85-2.29).³⁹

Other Enteric Infections

The “gastric bactericidal barrier” is thought to reflect mainly the low pH, because other constituents of the gastric juice seem to contribute little to the barrier function.⁴⁰ Indeed, the concept of “gastric bactericidal barrier” was introduced many decades ago. In 1934, Hurst stated that “the Services would have saved much invaliding if men with achlorhydria were not sent to the tropics” on the basis of observations that dysentery and similar infections were over-represented in people with impaired gastric acid secretion.⁴¹ A prolonged gastric acid inhibitor-induced hypochlorhydria has been suggested as a risk factor for severe gastrointestinal infections.^{42,43,68,69} Recent pediatric population data showed an increased risk of acute gastroenteritis (OR 3.58; 95% CI, 1.87-6.86) and pneumonia (OR 6.39; 95% CI, 1.38-29.70) in subjects using acid-suppressive drugs.⁴⁴ A systemic review conducted by Leonard et al³⁹ showed an increased risk of taking acid suppressors in those with enteric infections (OR 2.55; 95% CI, 1.53-4.26). The association was greater for PPI use (OR 3.33; 95% CI, 1.84-

6.02) compared with H₂-receptor antagonist use (OR 2.03; 95% CI, 1.05-3.92).³⁹ Table 3 enlists major studies performed to assess the increased risk of enteric infections with the long-term use of acid-suppressive therapy.

Pneumonia

Gastric acid suppression with H₂ blockers and PPIs is frequently used in critical care units as prophylaxis for stress ulcers. A meta-analysis published by Cook et al⁴⁵ in 1996 showed that H₂ receptor antagonists (eg, cimetidine and ranitidine together) are more effective than placebo for this clinical indication. However, there has always been concern of increased respiratory tract infections, such as pneumonia, especially in ventilator-dependent patients. In earlier studies comparing sucralfate with H₂ blockers, it was found that fewer respiratory tract infections are associated with the cytoprotective agent.^{46,47} Subsequent studies confirmed the association of acid suppression with pneumonia, especially in critically ill patients. The use of stress ulcer prophylaxis was recently challenged. In an observational study by Faisy et al,⁴⁸ stress-ulcer prophylaxis did not influence the clinically significant gastrointestinal bleeding rate in intensive care unit patients or the cost of its management. A recent randomized, placebo-controlled study of 287 patients with high risk for stress-related upper gastrointestinal hemorrhage (>48 h mechanical ventilation, coagulopathy) revealed significant stress-related upper gastrointestinal bleeding observed in 1%, 3%, 4%, and 1% of patients assigned to receive omeprazole, famotidine, sucralfate, and placebo, respectively ($P > .28$). Bleeding developed significantly more often in patients with coagulopathy compared with the others (10% vs 2%; $P = .006$). The study did not show that omeprazole, famotidine, or sucralfate prophylaxis can affect the already low incidence of clinically important stress-related bleeding in high-risk patients in surgical intensive care units. Furthermore, the data suggested that gastric pH-increasing medications could increase the risk for nosocomial pneumonia. On the basis of these data, routine prophylaxis for stress-related bleeding even in high-risk patients seems not to be justified.⁴⁹ A meta-analysis performed by Messori et al⁵⁰ showed ranitidine to be ineffective in the prevention of gastrointestinal bleeding in patients in intensive care and might increase the risk of pneumonia. These findings are based on small numbers of

patients, and firm conclusions cannot presently be proposed. In 2004, a large nested case-control analysis of more than 300,000 individuals was performed. The incidence rates of pneumonia in non-acid-suppressive drug users and acid-suppressive drug users were 0.6 and 2.45 per 100 person-years, respectively. The adjusted relative risk for pneumonia among persons currently using PPIs compared with those who stopped using PPIs was 1.89.²⁸

The risks of various infections associated with long-term PPI use have been demonstrated in different studies. However, the results need to be interpreted cautiously, because the studies are limited by their retrospective design and smaller size. Although gastric acid suppression has been postulated to be the cause of increased infections secondary to loss of defense mechanism and proliferation of pathogenic bacteria, it must be kept in mind that none of the PPIs truly increase intragastric pH >4 for a period of 24 hours. In fact, all of the current PPIs, if given in once-daily dose, maintain intragastric pH >4 only between 9 and 15 hours per day. Until the availability of large prospective studies, the risks of various infections, especially *C. difficile*, other enteric infections, and pneumonia associated with long-term PPI use cannot be firmly established.

Fundic Gland Polyps and Gastric Cancers

Fundic gland polyps are the most common gastric polyps. They are found in up to 1.9% of the general population and in up to 84% of patients with familial adenomatous polyposis. Fundic gland polyps have been regarded as benign lesions, with at most low-grade dysplasia (intraepithelial neoplasia). There have, however, been case reports of fundic gland polyps harboring severe dysplasia or even gastric adenocarcinoma when associated with familial adenomatous polyposis.⁵¹ The potential association of fundic gland polyps with the use of PPIs has long been a topic of debate. In 1992, 3 cases of fundic gland polyps that developed after 1 year of treatment with omeprazole were reported.⁵² Subsequently, a case-control study in patients with familial adenomatous polyposis suggested an increased risk of dysplasia in fundic gland polyps during PPI use and recommended routine endoscopies in patients receiving long-term PPI therapy to monitor fundic gland polyps development.⁵³ Increased risk of fundic gland polyps (OR 2.2; 95% CI, 1.3-3.8) with long-term use (>1 year) of PPIs compared with short-term use (OR 1.0; 95% CI, 0.5-1.8) was shown by another case-control study of 599 patients.⁵⁴ The exact cause of sporadic fundic gland polyps is unknown, although an association with β -catenin gene mutations has been described.⁵⁵ Dysplastic changes in fundic gland polyps developing during PPI therapy are rare and have only been reported in a few cases, despite the frequency of these polyps during PPI therapy.

Profound acid-suppressive therapy leads to hypergastrinemia in nearly all patients.⁵⁶ In rats, prolonged hypergastrinemia as a result of profound acid suppression results in hyperplasia of enterochromaffin-like cells. This can ultimately lead to gastric carcinoid formation. However, this

phenomenon has never been observed in other species. In humans, diffuse, linear, or micronodular hyperplasia of enterochromaffin-like cells is observed in 10% to 30% of chronic PPI users. This finding is most commonly seen in *Helicobacter pylori*-positive patients with more markedly increased gastrin levels. Dysplasia or invasive carcinoid formation has never been described in long-term PPI users and thus is not an indication for surveillance in PPI maintenance users.

More recently, interest has shifted to PPIs and associated gastritis changes instead of hypergastrinemia. In subjects in whom acid production is intact, *H. pylori* predominantly colonizes the gastric antrum. This colonization pattern is associated with an antral predominant gastritis. Inflammation of the antral mucosa stimulates gastrin secretion, which maintains acid production at a normal to high level and thus keeps the pattern intact. In contrast, in subjects in whom acid production is decreased by whatever mechanism, including the use of PPIs, *H. pylori* also colonizes the body of the stomach, leading to a corpus predominant gastritis. Inflammation of the gastric corpus mucosa further impairs acid secretion despite the increase in gastrin as a result of both the concomitant inflammation of the antrum and the reduction in acid secretion that continues as a cycle. The occurrence of body gastritis with impairment of parietal cell function augments the acid-suppressive effect of PPIs.⁵⁷ Several studies also have addressed the fact that profound acid-suppressive therapy can be associated with bacterial overgrowth with non-*Helicobacter* species within the stomach.⁵⁸ This bacterial overgrowth has been associated with more severe gastritis and increased serum cytokine levels. The clinical importance of these observations remains to be evaluated. In particular, it is not known whether bacterial overgrowth is a consequence of atrophic gastritis in PPI users or a contributing etiological factor.

The long-term consequences, particularly with respect to the risk of gastric cancer development, require further study. The available cohort studies in chronic PPI users do not provide data with gastric cancer as the end point. This can be explained simply by the lack of sufficient power of those studies with respect to both the number of subjects included and the period of follow-up. In the absence of such controlled cohort data, one may look for observational data from large population databases. One such database is the Dutch Integrated Primary Care Information database. This general practice research database contains the computer-based medical records of more than 500,000 patients in The Netherlands. This dynamic database was started in 1992 and contains the records of 27,328 patients who used at least 1 PPI prescription. During 8 years of follow-up, 45 (0.16%) were diagnosed with gastric cancer compared with 22 (0.01%) gastric cancer cases among 358,000 subjects not using a PPI followed for at least 1 year.⁵⁹

PPI therapy affects the pattern and severity of *H. pylori* gastritis and accelerates the process of corpus gland loss. At present, there is no evidence to suggest that this increases the risk of gastric cancer. There are, however, limited cir-

cumstantial data from both Japan and Europe that persistent corpus predominant gastritis and atrophy are major risk factors for the development of gastric cancer.^{59,60} *H. pylori* eradication can partially prevent and reverse these effects without impairing PPI therapy for gastroesophageal reflux disease. For these reasons, in 2005, the Maastricht consensus panel advised consideration of *H. pylori* eradication in patients who require long-term PPI therapy.

Colon Cancer

Hypochlorhydria leads to increased secretion of the peptide hormone gastrin from the gastric antrum. Gastrin has trophic effects on tissues throughout the gastrointestinal tract.⁶¹ High gastrin levels are associated with the growth and proliferation of colon cancer cells in culture.⁶² Patients with hypergastrinemia secondary to Zollinger-Ellison syndrome have been shown to have increased rectal mucosa proliferation.⁶³ A case-control study that used frozen sera suggested that a baseline gastrin level above normal was associated with a 4-fold increased risk of colorectal carcinoma.⁶⁴ However, a recent population-based case-control study conducted by Robertson et al⁶⁵ found no increased risk of colorectal carcinoma in patients taking PPIs. The clinical significance of the trophic effects of long-term PPI-related hypergastrinemia on colon polyps was studied by Singh et al,⁶⁶ who found no influence on the frequency, growth, or histology of adenomatous polyps. More recently, a large case-control study evaluating the risk of colorectal carcinoma in more than 457,000 patients taking PPIs did not show any increased risk in the PPI group.⁶⁷

Thus, despite significant theoretic and in vitro data suggestive of an increased risk for colorectal carcinoma with elevated gastrin levels, no clinically significant increased risk of malignancy or increased number or size of adenomatous polyps has been shown.

CONCLUSIONS

PPIs are highly effective drugs that have revolutionized the management of acid-related disorders during the last 2 decades. Although the long-term use of PPIs seems to have a high margin of safety, concerns have been raised about the potential risks after long-term use.

Although several studies have investigated the potential effect of PPI therapy on vitamin B₁₂ absorption, a firm association cannot be established. The studies are limited by their smaller size and retrospective design. Currently, monitoring of B₁₂ levels in patients receiving long-term PPI therapy cannot be recommended until further prospective randomized trials confirm the association.

Despite the theoretic considerations, there are relatively little data to indicate that PPI therapy causes iron deficiency. There are no data that PPI use under normal clinical circumstances results in iron deficiency. Routine monitoring of iron levels is not recommended. However, care should be taken in prescribing PPIs to patients who are already iron

depleted, and adequate supplementation with iron should be considered.

The studies examining the impact of PPIs on calcium absorption are limited by several factors, including the use of indirect methods to assess calcium absorption and disease states that could influence mineral metabolism, such as renal failure. Similarly, few case-control studies have suggested an association with increased risk of fracture. However, the studies are limited by a low magnitude of association (OR <2) and a lack of experimental evidence documenting a mechanism. Also, the inability to assess potential confounding factors in the studies limit statements regarding causality. As with all medications, PPIs should be used for appropriate indications and in appropriate doses. Therefore, recommendations to discontinue therapy because of potential increased risk of osteoporosis in patients taking PPIs for appropriate indications and in appropriate doses cannot be made at the present time.

Increased risk of enteric infections, including *C. difficile*, has been suggested in recent systemic review of gastric acid-suppressive drugs. However, the majority of studies are hospital based, and improper choice of controls may contribute to the discrepant results. Judicious use of these agents should be carried out, especially in hospitalized patients. With increasing use of PPIs, the aging population, and increasing concerns of multiresistant pathogens, continued research in this area is critical.

Similarly, a theoretic risk of increased gastric and colon cancer associated with long-term PPI use has not been validated in prospective randomized trials, and future trials in this area are required to firmly establish the association. Until then, PPIs cannot be associated with an increased malignancy risk. Efforts should be made, however, to minimize unnecessary and inappropriate use of PPIs to reduce the potential associated risks and health care costs.

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