Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications

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Abstract: Proton pump inhibitors (PPIs) remain the superior choice worldwide in antisecretory therapy in the evidence-based treatment of upper gastrointestinal disorders including gastroesophageal reflux disease, erosive esophagitis, dyspepsia and peptic ulcer disease. PPI overutilization 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. Nonjudicious use of PPIs creates both preventable financial as well as medical concerns. PPIs have been associated with an increased risk of vitamin and mineral deficiencies impacting vitamin B_{12}, vitamin C, calcium, iron and magnesium metabolism. While these risks are considered to be relatively low in the general population, they may be notable in elderly and malnourished patients, as well as those on chronic hemodialysis and concomitant PPI therapy. No current evidence recommends routine screening or supplementation for these potential vitamin and mineral deficiencies in patients on either short- or long-term PPI therapy. Reducing inappropriate prescribing of PPIs can minimize the potential risk of vitamin and mineral deficiencies.

Keywords: antisecretory therapy, calcium, iron, magnesium, mineral deficiency proton pump inhibitor(s), vitamin B_{12}, vitamin C, vitamin deficiency

Introduction

Evidence-based guidelines supporting proton pump inhibitor (PPI) use as the superior option for antisecretory therapy (AST) for treatment of non-erosive gastroesophageal reflux disease (GERD), erosive esophagitis, dyspepsia and peptic ulcer disease have guided clinicians in the treatment of these conditions since their inception in the 1980s, while demonstrating dramatically improved symptomatic outcomes in large numbers of patients [DeVault and Castell, 2005; Kahrilas *et al.* 2008; University of Michigan Health System, 2012]. The PPIs continue to be universally heralded as a safe pharmacotherapeutic option with an extremely low theoretical risk of the development of gastric cancer secondary to hypergastrinemia and achlorhydria [Poulsen *et al.* 2009].

The strong evidence supporting PPI efficacy, as well as a favorable safety profile, may have contributed to the widely held concern that PPIs are overutilized. Moreover, the practice of PPI overutilization is considered a direct result of the lack of determination of need for continuous therapy in many nonhospitalized patients. Substantial expenditure on PPIs has led researchers to create cost-effective and evidence-based paradigms of treatment strategies for GERD, including on-demand and step-down therapy, yet even after a decade of conception few clinicians follow such guidelines [Inadomi, 2002; Inadomi *et al.* 2003; Metz *et al.* 2007]. It has also been proven that PPIs are substantially overutilized for stress ulcer prophylaxis in nonintensive care unit patients, leading to significant yet controllable cost expenditure both in the hospital setting and after discharge [Heidelbaugh and Inadomi, 2006; Pham *et al.* 2006].

Cost utilization data from 2010 show that brand name PPIs accounted for ~US$7.2 billion and generic PPIs accounted for ~US$2.5 billion in US sales, with Nexium® (esomeprazole; Astra Zeneca) ranking first in brand name prescription

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expenditure and pantoprazole and omeprazole both ranking in the top five in generic prescription expenditure [Drug Topics, 2012a, 2012b]. Approximately 80% of PPIs in the US are purchased without either a prescription or physician evaluation of upper gastrointestinal symptoms [Heidelbaugh *et al.* 2009a].

The last decade has produced landmark publications across multiple specialties including primary care, managed care, gastroenterology and pharmacology highlighting the potential risks associated with nonjudicious and inappropriate short- and long-term use of PPIs in both hospital and ambulatory care practices [Heidelbaugh *et al.* 2009a, 2009b]. The reported adverse effects associated with PPIs include an increased risk of enteric infections including *Clostridium difficile*-associated diarrhea [Aseeri *et al.* 2008; Jayatilaka *et al.* 2007; Dial *et al.* 2005; Yearsley *et al.* 2006]; community-acquired pneumonia [Laheij *et al.* 2004; Gulmez *et al.* 2007; Sarkar *et al.* 2008]; altered metabolism of antiplatelet agents (e.g. clopidogrel) [Gilard *et al.* 2008; Siller-Matula *et al.* 2009; Small *et al.* 2008; Ho *et al.* 2009]; osteoporotic-related fracture, and interference with vitamin and mineral absorption and metabolism. The latter concern has received underwhelming attention in the general public until the US Food and Drug Administration (FDA) issued warnings in 2010 and 2011 postulating a relationship between long-term PPI use and osteoporosis-related fracture and hypomagnesemia, respectively [FDA, 2010, 2011].

A computerized literature search was performed using the MEDLINE database from 1966 through October 2012 to identify all publications using the following terms: proton pump inhibitor(s), vitamin/mineral deficiency, vitamin/mineral malabsorption, vitamin B_{12}, vitamin C, calcium, iron and magnesium. The search was limited to studies involving human subjects published in the English language. Abstracts and book chapters were excluded from the search, although case studies were included given the specificity and nature of the search topics. Bibliographies from index citations were reviewed for additional relevant studies.

Mechanism of action

PPIs are the most potent inhibitors of gastric acid secretion, with a potential to increase intragastric pH by several units, as well as hydrogen ion concentration by several hundred to thousand fold [McColl, 2009]. Their mechanism of action centers on inhibition of the H^+/K^+ ATPase enzyme in gastric mucosal parietal cells, which is responsible for hydrogen ion secretion in exchange for potassium ions in the gastric lumen [Sheen and Triadafilopoulos, 2011]. As a result, PPIs can modify the bioavailability and absorption of essential vitamins and minerals both in the stomach and duodenum, which may also affect more distal absorption. Recent case reports and retrospective literature reviews have posited a potential adverse association between both short- and long-term PPI utilization and vitamin and mineral deficiencies. At present time, the clinical significance of this hypothesis remains largely unknown with regard to extrapolation to every day clinical practice, given a lack of large cohort, rigorous, prospective, outcomes-based trials examining both associated risk(s) and clinical symptomatology.

Vitamin deficiencies

Vitamin B_{12}

Vitamin B_{12} (cobalamin) is an essential water-soluble nutrient acquired from animal-derived food sources including meats, fish, shellfish, poultry, eggs and dairy products. Lacto-ovo vegetarians are generally not considered to be at risk for deficiency, while true vegans may risk deficiency unless they consume supplements or vitamin B_{12} fortified foods including cereals and soy-based products. Since the common human diet contains substantially more vitamin B_{12} than is required, a large functional reserve with respect to vitamin B_{12} absorption is assumed [Howden, 2000].

Vitamin B_{12} absorption involves peptic enzymes to cleave dietary B_{12} from dietary proteins. This is performed primarily by pepsin, which requires gastric acid to activate it from its pepsinogen precursor. Without gastric acid, vitamin B_{12} would not be cleaved from dietary protein and would not be able to bind to R-proteins, which in turn protect vitamin B_{12} from pancreatic digestion [Festen, 1991]. It has been hypothesized that since gastric acidity is required for vitamin B_{12} absorption, acid suppression may lead to malabsorption and ultimately vitamin B_{12} deficiency from atrophic gastritis and achlorhydria [Howden, 2000].

It has been estimated that vitamin B_{12} deficiency affects up to 20% of the elderly, and has been linked to impaired gastrointestinal absorption

syndromes and pernicious anemia [Andres *et al.* 2004]. Most clinical cases are undetected and are found incidentally, while more profound cases may present with neuropsychiatric and hematologic findings (e.g. macrocytic anemia) that may be a harbinger of more severe underlying disease. The reduction in upper small intestine gastric acid *via* PPI therapy may promote bacterial overgrowth allowing for increased bacterial consumption of cobalamin, but the clinical correlation of adverse effects on nutritional status has never been determined.

Studies to date that have evaluated the relationship between PPI use and vitamin B_{12} deficiency are predominantly case reports and cross-sectional observational trials. The results from these trials have not yielded consistent data to create either therapeutic guidelines or to offer recommendations for routine dietary supplementation. In a systematic review by Sheen and Triadafilopoulos, the authors summarize experimental evidence suggesting that PPIs reduce the absorption of protein-bound vitamin B_{12} while not completely inhibiting the process, yet PPI therapy does not statistically affect the absorption of unbound and bound vitamin B_{12} [Sheen and Triadafilopoulos, 2011; Koop, 1992; Schenk *et al.* 1996].

The initial concern regarding the risk of vitamin B_{12} deficiency due to long-term AST use is derived from a prospective trial in patients with Zollinger–Ellison syndrome (ZES). A trial of 131 patients treated with either omeprazole (n = 111; mean 4.5 years) or histamine H2 receptor antagonist (H2RAs; n = 20; mean 10 years), determined that serum vitamin B_{12} levels were significantly lower in patients treated with omeprazole (p = 0.03), especially in subjects with omeprazole-induced sustained hyposecretion (p = 0.0014) or complete achlorhydria ($p < 0.0001$), while serum folate levels were not statistically affected [Tremanini *et al.* 1998]. In 68 patients with two vitamin B_{12} assays obtained 5 years apart, serum levels were decreased by 30% in patients who were achlorhydric (p = 0.001). The duration of omeprazole treatment was found to be inversely correlated with serum vitamin B_{12} levels (p = 0.013), but not with serum folate levels.

Trials from early last decade have demonstrated a more likely association with PPIs and vitamin B_{12} deficiency. A case-control study in Medicaid patients evaluated 125 patients with vitamin B_{12} deficiency compared with 500 control subjects [Force *et al.* 2003]. More than 18% of patients who received vitamin B_{12} supplementation had been given AST with either PPIs or H2RAs over a 12-month period compared with 11% in the control group (odds ratio [OR] = 1.82; p = 0.025). Another case-control study in a US university-based geriatric primary care setting identified 53 patients with cobalamin deficiency and compared them with 212 controls with respect to past or current use of prescription AST [Valuck and Ruscin, 2004]. The relative risk of vitamin B_{12} deficiency associated with AST for <12 months was 1.03 (95% confidence interval [CI] = 0.46–2.31), while that for ≥12 months was 4.46 (95% CI = 1.49–13.3). With an estimated baseline 5% risk of vitamin B_{12} in the elderly in this trial, the number needed to harm (NNH) is 7; with an assumed baseline risk of 10% deficiency, the NNH is 4.

Ito and Jensen recently summarized the results of more recent trials examining vitamin B_{12} deficiency risk due to PPI therapy in a systematic review [Ito and Jensen, 2010]. One case-control study involving 125 long-term (greater than 3 years) PPI users from general practices who were aged 65 years or older, compared with the same number of controls [den Elzen *et al.* 2008]. Vitamin B_{12} deficiency status was determined by measurement of serum vitamin B_{12} and homocysteine levels, as well as red blood cell mean corpuscular volume. This trial found no significant association between long-term PPI use and vitamin B_{12} status between the two groups. A longitudinal study of 61 acid hypersecretors, 46 of whom had ZES and all of whom were taking long-term PPI therapy, were followed for up to 18 years to determine risk of vitamin B_{12} malabsorption [Hirschowitz *et al.* 2008]. Of 61 patients, 10% had low serum vitamin B_{12} levels, while further investigation discovered vitamin B_{12} deficiency 31% patients despite normal serum vitamin B_{12} levels. Lastly, a cross-sectional study evaluated the effects of chronic use of H2RAs (150 patients), PPIs (141 patients) or no AST (251 patients) in patients in nursing homes or community ambulatory care facilities aged 60 to 102 years over a period of 6 or more years [Dharmarajan *et al.* 2008]. Decreased serum vitamin B_{12} levels were discovered in 20% of the nursing home patients and 29% of the community care patients at baseline. While PPI use was correlated with lower serum vitamin B_{12} levels, H2RA use was not.

A recent study by Rozgony and colleagues prospectively examined trends in serum vitamin B_{12} levels in 36 long-term care residents aged 60 to 89 years, 17 of whom were on chronic PPI therapy [Rozgony *et al.* 2010]. The authors found a statistically significant difference in mean serum vitamin B_{12} and methylmalonic acid levels and frequency of vitamin B_{12} deficiency at baseline between long-term PPI users compared with nonusers (75% *versus* 11%, $p = 0.006$). The PPI users were subsequently given 8 weeks of intranasal vitamin B_{12} nasal spray dosed at 500 µg weekly. Follow-up evaluation concluded that serum vitamin B_{12} levels then increased ($p = 0.012$), while the frequency of vitamin B_{12} deficiency decreased ($p = 0.004$).

While some data suggest an increased risk of vitamin B_{12} deficiency with PPI use, most current evidence is based upon small, poorly controlled and nonrandomized studies and case reports. Assumption of increased risk of vitamin B_{12} deficiency in the elderly and malnourished may be likely to some degree, but there is no evidence to suggest additional supplementation or monitoring of serum cobalamin levels. Prospective trials, with patient recruitment at the commencement of PPI therapy, are needed to prove a direct cause-and-effect relationship of vitamin B_{12} deficiency.

Vitamin C

A recent review by McColl highlights a detailed understanding of the effect of PPIs on vitamin C absorption [McColl, 2009]. Humans are unable to synthesize vitamin C and thus must rely upon obtaining adequate concentrations of the water-soluble vitamin from dietary intake. PPIs affect its bioavailability *via* lowering its concentration in gastric juices as well as the proportion of vitamin C in its active antioxidant form, ascorbic acid. The ascorbic acid that is in turn secreted by the gastric mucosa directly affects the concentration of nitrite and iron in gastric juices.

Mowat and colleagues investigated the effects of omeprazole 40 mg for 4 weeks on vitamin C concentrations in gastric juice in healthy individuals [Mowat *et al.* 1999]. Median intragastric pH increased from 1.4 prior to omeprazole therapy to 7.2 (range 3.5–8.5) while subjects were taking omeprazole, and vitamin C concentrations decreased from 5 µm/l pretreatment with omeprazole to 3 µm/l while subjects were taking omeprazole, reflecting a notable decrease in the biologically active form of ascorbic acid. The clinical significance relative to the decreases in vitamin C is derived from a theory that it may protect against conversion of nitrite to *N*-nitroso compounds by bacteria which could potentially colonize the achlorhydric stomach environment.

There is additional evidence that PPIs lower serum vitamin C concentrations, an effect more prominently noted in patients who were infected with *Helicobacter pylori* [Mowat *et al.* 1999; Henry *et al.* 2005]. Authors of these trials have postulated that the gastritis in the body of the stomach secondary to *H. pylori* infection taking a PPI (omeprazole in these studies) may increase vitamin C metabolism leading to systemic depletion. The clinical significance of this effect remains unknown, and vitamin C supplementation is not currently recommended in patients taking PPIs or in those being treated for *H. pylori* infection.

Mineral deficiencies

Calcium

A review by Insogna provides the framework upon which to understand the relationship between PPI therapy and calcium metabolism [Insogna, 2009]. It has been proposed that both stomach acid and the slightly acidic milieu of the proximal duodenum are necessary in order to dissociate ingested calcium from a food bolus rendering it available for absorption. Without this environment, elemental calcium would not be absorbed, potentially leading to compensatory physiologic changes including secondary hyperparathyroidism. While there is conflicting evidence with regard to the role of intragastric hydrochloric acid in calcium absorption, and PPIs are known to inhibit this mechanism, one study found that gastric acid secretion and gastric acidity do not normally play a role in the absorption of dietary calcium [Bo-Linn *et al.* 1984]. PPIs reduce resorption of calcium from bone, as osteoclasts also possess proton pumps, thus their activity is thought to be directly affected by PPIs [Farina and Gagliardi, 2002].

Many studies examining the impact of PPIs on intestinal calcium absorption are limited by the evaluation of patients with renal failure on hemodialysis or those with hypo- or achlorhydria, two chronic conditions known to adversely affect calcium metabolism [Insogna, 2009]. Several short-term trials with small numbers of

subjects evaluating the effects of PPIs on intestinal calcium absorption found no significant increase in serum calcium during PPI therapy, consistent with decreased calcium absorption [Hardy *et al.* 1998; Graziani *et al.* 2002; O'Connell *et al.* 2005]. One particular study, in postmenopausal women who received calcium supplementation taken on an empty stomach, did not demonstrate decreased calcium resorption with concomitant PPI utilization [O'Connell *et al.* 2005].

To date, no long-term prospective, randomized, controlled trials exist to examine the potential increased risk of bone fracture associated with concomitant PPI use, as all published data is derived from retrospective case-controlled, cohort and cross-sectional studies. A series of trials implicating PPI therapy as leading to an increased risk of osteoporotic fracture has stimulated a critical analysis of the possible relationship, suggesting a causal relationship [Yang *et al.* 2006; Vestergaard *et al.* 2006; Targownik *et al.* 2008; Kaye and Jick, 2008; Gray *et al.* 2010]. Newer research offers conflicting data, implying that study subjects who had been on PPI therapy may be at a higher risk of osteoporotic fracture compared with an individual at average risk, yet the authors concluded that PPI use was not associated with a change in bone mineral density [Targownik *et al.* 2010].

In 2010, the US Food and Drug Administration released a warning revising the prescription and over-the-counter (OTC) labels for PPIs to include new safety information regarding a potential increased risk of fractures of the hip, wrist and spine with the use of these medications [FDA, 2010]. This warning was updated in 2011, as the FDA determined that an osteoporosis and fracture warning on the OTC PPI 'Drug Facts' label is not indicated, concluding that fracture risk with short-term, low-dose PPI therapy is unlikely [FDA, 2011]. Patients felt to be at highest risk for fractures had either received high doses of prescription PPIs (higher than OTC PPI doses) or had used a PPI for 1 year or more, or both.

Iron

It has been postulated that chronic PPI therapy results in clinically significant iron malabsorption due to gastric acid hyposecretion and the risk of achlorhydria. Dietary iron is present in food as either nonheme (66%) or heme iron (32%) and absorption of nonheme iron is markedly improved by gastric acid. Gastric acid assists food sources containing nonheme iron to dissociate and to solubilize the iron salts, allowing formation of complexes with sugars and amines facilitating absorption [Ito and Jensen, 2010].

While many patients with a history of vagotomy, gastric resection or atrophic gastritis have been shown to have iron deficiency anemia, a cohort of patients with ZES who received treatment with PPIs for over 10 years did not demonstrate clinically significant iron deficiency [Stewart *et al.* 1998]. Several case reports have suggested an association between PPI use and iron deficiency anemia, with subjects not responding to iron replacement while on concomitant PPI therapy but responding favorably when PPI therapy was stopped [Sharma *et al.* 2004; Hutchinson *et al.* 2007].

A retrospective cohort study of adult patients in an academic outpatient setting who received PPI therapy for at least 1 year sought to evaluate any potential change in hematologic indices against matched controls [Sarzynski *et al.* 2011]. Of the 98 patients who met inclusion criteria, PPI users were observed to have significant decreases in mean hemoglobin and hematocrit concentrations ($p < 0.01$ for both parameters) compared with matched controls. After adjustment for confounders including invasive evaluation, the odds ratio of decreasing hemoglobin by 1.0 g/dl while on chronic PPI therapy was 5.03 (95% CI = 1.71–14.78, $p < 0.01$), while the odds ratio of decreasing hematocrit by 3% was 5.46 (95% CI = 1.67–17.85, $p < 0.01$). Of the PPI users in this trial, 35% had no documented appropriate indication for such therapy, similar to results in previous ambulatory care setting trials [Heidelbaugh *et al.* 2010]. Despite these results, there is no current recommendation to monitor patients on chronic PPI therapy for iron deficiency anemia.

Magnesium

Hypomagnesemia secondary to chronic PPI therapy is now a well-documented yet still rare phenomenon, as to date there is no widely accepted mechanism to explain such an association. One researcher posited that it may occur in cases of 'poor metabolizers' of PPIs, but this has been disproven [Hoorn *et al.* 2010]. Hypomagnesemia has been documented with all PPIs that are biochemically substituted pyridylmethylsulphonyl benzimidazadole derivatives (in order of potency: rabeprazole, esomeprazole, omeprazole, lansoprazole and pantoprazole). While several trials have documented recurrence of hypomagnesemia

when one PPI is substituted for another, it considered as a class effect [Cundy and Mackay, 2011].

Fewer than 30 cases of hypomagnesemia have been described in the literature associated with PPI therapy since 2006, with 61% having received PPI therapy for 5 or more years and 29% for at least 10 years [Sheen and Triadafilopoulos, 2011]. The median age at diagnosis was 70 (range 51–82) and deficiency was reported more frequently in women than men. Most patients with suspected PPI-induced hypomagnesemia presented with concomitant hypokalemia and hypocalcemia, as well as severe ataxia, paresthesias, seizures, confusion and gastrointestinal symptoms requiring hospitalization. In these patients, there was no evidence of magnesium malabsorption, renal wasting or histological abnormalities on small intestinal or colonic biopsies. The most severe symptoms have been associated with the lowest plasma magnesium and calcium concentrations [Cundy and Mackay, 2011].

In 2011, the FDA released a warning based upon several published case reports stating that PPIs may cause hypomagnesemia if taken for longer than a year [FDA, 2011]. In approximately 25% of cases reviewed, magnesium supplementation alone did not adequately increase serum magnesium levels and thus PPI therapy had to be discontinued. It is considered to be reasonable practice to screen patients with a history of cardiac arrhythmias or those on antiarrhythmic agents for low serum magnesium if they are on chronic PPI therapy.

Gau and colleagues conducted a cross-sectional study to determine the potential effects of PPI therapy relative to development of hypomagnesemia [Gau *et al.* 2012]. Data from 207 hospitalized adults on PPI therapy aged over 50 years who had measurement of serum magnesium revealed that both standard and high-dose PPI use was associated with an increased risk of hypomagnesemia (adjusted OR = 2.50, 95% CI = 1.43–4.36), suggesting a subclinical insufficiency or deficiency status in asymptomatic individuals.

Future direction

PPIs will continue to be the predominant form of AST for the treatment of many upper gastrointestinal conditions. Judicious and appropriate use of these medications will be imperative to minimize both the theoretical and actual risk of vitamin and mineral deficiencies. Future research will require a focus on various populations across all ages to continue to screen for vitamin and mineral deficiencies, balancing the cost-effectiveness of both serologic testing and ongoing pharmacotherapy.

Conclusion

PPIs have revolutionized the therapy of numerous upper gastrointestinal tract disorders, while posing a very minute and largely theoretical risk of adverse effects based upon data from mostly small retrospective trials. The overall benefits of therapy and improvement in quality of life significantly outweigh potential risks in almost all patients. Risk stratification of elderly, frail, malnourished, dialyzed and chronically hospitalized patients should direct clinicians to measure benefits of therapy against risks. It is paramount for clinicians to reassess their individual patient's needs for continuation of PPI therapy long-term, minding cost-effective prescribing practices. Prospective trials are needed to more firmly establish direct cause-and-effect relationships between PPIs and adverse events through either discontinuation or withdrawal of compared with subjects who remain on therapy.

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Conflict of interest statement

The author declares no conflicts of interest in preparing this article.

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