PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Reported Side Effects and Complications of Long-term Proton Pump Inhibitor Use: Dissecting the Evidence

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This article has an accompanying continuing medical education activity on page e38. Learning Objectives—At the end of this activity, the successful learner will be able to analyze the literature base around reported complications of proton pump inhibitor therapy and provide evidence-based recommendations for patient care.

Podcast interview: www.gastro.org/cghpodcast. Also available on iTunes.

Proton pump inhibitors (PPIs) are medications that are ubiquitous in a 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 (H2RA) for patients with moderate to severe gastric acid–related diseases as well as for prophylaxis of upper gastrointestinal (GI) injury (eg, with nonsteroidal anti-inflammatory drugs). The success of these drugs, with sales totaling approximately $13.6 billion worldwide in 2009,[1] is not just a result of their potency and effectiveness in improving symptoms and complications of acid-peptic diseases. Their safety among pharmacologic agents has been unparalleled as one of the safest classes of medications that gastroenterologists deal with, however, despite this there have been emerging concerns with reports of potential adverse effects associated with use of PPIs. In the United States, such reports have led the Food and Drug Administration (FDA) to issue a number of broad-based product warnings, including all of the available PPI drugs either for prescription or over-the-counter purchase. 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 and related drug interactions, or alterations of intended effect, 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, and provides the authors' bottom-line recommendations for clinical practice.

Effects on Vitamin and Mineral Absorption

Iron

Nonheme iron (ferric, Fe^{3+}) constitutes the majority of dietary iron consumed. To be absorbed by duodenal enterocytes, this iron subsequently must undergo a reduction into the ferrous state (Fe^{2+}), mediated by hydrochloric acid released from the stomach. In vivo data have shown that this absorption is related directly to the release of ferric iron by gastric juice.[2] There also 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.[3] 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 absorption to be clinically apparent.[4,5] 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.[6]

To date, only one study has addressed the association between PPI use and the development of iron-deficiency anemia. This study found that among patients receiving chronic PPI therapy there was a significant decrease in all hematologic indexes from baseline.[7] Despite these findings, the study suffered from a number of drawbacks including small sample size, limited serial ferritin levels to properly determine iron-deficiency anemia, and the inability to exclude a number of potential confounders. Given these limitations, this study did not offer a definitive answer on the topic.

Bottom line. Although it is conceivable that PPI therapy may reduce absorption of nonheme iron and retard iron pool replenishment, this effect has not been well studied or evident from widespread use in clinical practice.

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 hypochlorhy-

Abbreviations used in this paper: BMD, bone mineral density; CAP, community-acquired pneumonia; CI, confidence interval; FDA, Food and Drug Administration; GI, gastrointestinal; H2RA, histamine 2–receptor antagonist; IBS, irritable bowel syndrome; OR, odds ratio; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; SIBO, small intestinal bacterial overgrowth.

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dric states, in particular those induced by PPIs, may impair calcium absorption; however, there are limited data to support this claim; in fact 2 high-quality studies showed no adverse effect.[8,9] Overall, the studies suggested that calcium absorption potentially was affected negatively only in the setting of reduced acid secretion when ingested calcium carbonate was provided in the fasting state. Despite this, 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 (ie, 2 weeks) for up to 3 cycles per year.[10]

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. In addition, the strength of association in the PPI studies has been of low magnitude. Given that the estimates and even the upper bounds of most of the 95% confidence intervals (CIs) of the odds ratios (ORs) were well below 2, there is a strong possibility these differences could have been related to the channeling bias inherent in observational studies.[11] For example, a prospective study including 79,899 postmenopausal women from the US Nurse's Health Study showed that despite an OR of 1.36 (95% CI, 1.13–1.63) for PPI use, when accounting for a history of smoking, there was no significant association between PPI use and fracture risk (OR, 1.06; 95% CI, 0.77–1.46).[12] More recent studies have shown an association between PPI use and hip fracture risk, yet there was no evidence to suggest a duration effect from long-term PPI use (OR, 1.30; 95% CI, 0.98–1.70) as compared with short-term use (OR, 1.24; 95% CI, 1.19–1.28).[13] This suggests that the observed association likely was owing to confounding factors. In addition, other recent cross-sectional, longitudinal, and prospective observational reports did not support the prior reported association.[14,15] Even more convincing evidence supporting the lack of harm comes from a recently published population-based sample of Canadians who underwent bone mineral density (BMD) testing of the femoral neck, total hip, and lumbar spine at baseline, and then again at 5 and 10 years. In all, 8340 subjects were included in the baseline analysis, with 4512 (55%) undergoing year 10 BMD testing. After adjusting for potential confounders, PPI use was associated with significantly lower baseline BMD at the femoral neck and total hip. By multivariate linear regression, however, there was no evidence of any acceleration in covariate-adjusted BMD loss at any measurement site after 5 and 10 years of follow-up evaluation. Therefore, PPI users had lower BMD at baseline than PPI nonusers, but PPI use over 10 years did not appear to be associated with accelerated BMD loss. It would be paradoxic that there would be an element of risk at entry and that longer duration of exposure would not amplify any risk effect.[16]

Contrary to their purported role in increasing the risk for fractures, PPIs actually may increase bone density through their impairment of osteoclast activity. Osteoclasts contain vacuolar proton pumps necessary for acidification at the ruffled border, which facilitates dissolution of the bone matrix and its subsequent resorption.[17] 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.[18]

Bottom line. There is no good evidence to establish that PPI use has a significant risk for bone density loss or osteoporotic-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.

Magnesium

There have been several (total, <50) cases of hypomagnesemia that were associated with long-term PPI use.[19–21] 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 rechallenged with a PPI, the hypomagnesemia recurred, suggesting a PPI-related effect. None of the patients had identifiable GI wasting or renal loss etiologies. A recent systematic review on this association concluded that there was no typical patient profile that was unique for PPI-related hypomagnesemia and the final attribution to the symptoms and electrolyte abnormalities sometimes took years; in the absence of symptoms, identification of PPI-related hypomagnesemia was purely dependent on chance.[22] In addition, data from this review further support a PPI class effect because there is evidence that subsequent treatment with H2RAs prevents the recurrence of hypomagnesemia. Together, these case reports prompted a recent alert by the FDA about PPI use and hypomagnesemia.[23] Although it originally only was cited for omeprazole and esomeprazole, it was later revised to cover PPIs as a class. This alert suggested that health care providers should consider checking magnesium levels in patients who are anticipated to be on long-term PPIs.

The mechanism for the magnesium depletion is not known. The primary absorption of magnesium is through a passive pathway in the small intestine. There is some identifiable active transport, however, via transport channels (transient receptor potential and magnesium transporter 6 and 7).[24] 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.

Bottom line. The FDA recommendation to consider checking magnesium levels before starting is not practical, in particular for the over-the-counter market. In patients who may be predisposed to present or ongoing magnesium loss from intestinal malabsorption or renal excretion and wasting, it may be reasonable to follow up magnesium levels more closely and consider this association, particularly if profound hypomagnesemia develops. 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 keep PPIs where clinically justified.

Vitamin B_{12}

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.

Bottom line. 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.[24,25] In addition, to date no studies have provided a longitudinal evaluation showing alterations of specific metabolic intermediates (eg, 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.[26]

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.[27] This reliance on the same pathway has led to the hypothesis that competition at CYP2C19 may reduce the biological activity of clopidogrel. This is supported by in vitro studies that showed a pharmacodynamic interaction, which was an attenuated antiplatelet effect as measured by adenosine diphosphate–induced platelet aggregation and increased platelet activity.[28] More recent evidence has suggested that this effect is related more closely to the reduced function of CYP2C19*2 and *3 alleles.[29,30] This is an important consideration when analyzing potential competition between PPIs and clopidogrel because these polymorphisms are quite prevalent, affecting 30% of whites, 40% of blacks, and 55% of East Asians.[31]

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.[32,33] 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.[34,35] 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.[36]

Despite the FDA's recommendation against specific PPIs, the most recent meta-analysis on the subject found no consistent evidence for intraclass differences among PPIs when used with clopidogrel.[37] Early studies suggested that pantoprazole, a less-potent inhibitor of CYP2C19, would have less of an effect on clopidogrel, and the current product labeling 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.[38] Despite this, combination therapy did not significantly increase the risk of adverse cardiovascular events. Another recent study comparing the potential antiplatelet interference effect on co-therapy of dexlansoprazole with clopidogrel showed bioequivalence to placebo and a product label change was made in May 2012 indicating that there was no physiological reduction in clopidogrel effect when these drugs were used concomitantly.[39]

A literature review suggests that the original reasons for the perceived intraclass differences most likely arose from a channeling bias—the tendency among physicians to prescribe certain medications for certain patient populations.[40,41] A cohort of 23,000 patients from the Veterans Administration Pharmacy Benefits Management Database showed that omeprazole was the most commonly prescribed PPI (88%), with esomeprazole, lansoprazole, rabeprazole, and pantoprazole accounting for the remainder.[42] 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.[40] In addition, a systematic review of 19 studies showed that considerable heterogeneity among the studies did not allow for the demonstration of a clear interaction between clopidogrel and PPIs in platelet function studies.[43]

Bottom line. The current literature questions the exact relationship between ex vivo platelet assays and clinical outcomes, especially with regard to the assessment of drug interactions. Although the platelet assays and observational data may be factual, they are not always appropriate for extrapolation into clinical care. 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.

Proton Pump Inhibitors and Infection

Pneumonia

Several studies have focused on assessing the risk between PPI use and community-acquired pneumonia (CAP) and hospital-acquired pneumonia. The initial case-control study of 5551 cases in The Netherlands found a relative risk for CAP among PPI users of 1.89 (95% CI, 1.32–2.62).[44] Subsequently, 2 other studies found a moderate risk of CAP in patients exposed to PPIs.[45,46] The most recent meta-analysis (9 studies, 120,863 patients) further delineated the relative risks of PPI use and CAP, finding that there was no association between CAP and PPI use longer than 180 days (OR, 1.10; 95% CI, 1.00–1.21); rather, the association between PPI use and CAP was strongest for PPI use of fewer than 30 days (OR, 1.65; 95% CI, 1.25–2.19) and high-dose PPIs (OR, 1.50; 95% CI, 1.33–1.68).[47] Also supporting the association between short-term PPI use and CAP, a database review of 71,985 outpatient prescriptions for PPIs in the New England Veterans Healthcare System found that PPI use between 1 and 15 days had increased risk for CAP over longer PPI exposures.[48]

Despite the results of these studies, other studies have found no significant increase in CAP risk from PPI use, long term or current.[49] A case-controlled review of 80,000 patients found that when accounting for potential confounding factors, there was no significant association between current PPI use and increased CAP (adjusted OR, 1.02; 95% CI, 0.97–1.08).[50] This highlights the influence of heterogeneity between studies and the potential influence of confounding factors on the results of the other studies.

Bottom line. Health care providers should be aware of the potential adverse relationship between PPI use and CAP, namely, a small relative risk associated with short-term and high-dose PPI use. These relationships, however, do not offer a definitive explanation for the relative risk because significant heterogeneity among studies and a number of confounding factors may have accounted for some of the observed statistical significance.

Clostridium Difficile

Previously, gastric acid was not believed to be important in protecting against *C difficile* infection because acid-resistant spores

were presumed to be the principal vector of transmission. Recently, this thought was challenged because several studies have found a higher risk of *C difficile* infection in PPI users. In theory, PPIs may increase the risk of *C difficile* infection by increasing the ability of the spore to convert to the vegetative form and to survive in the lumen of the GI tract. The data for community-acquired vs hospital-acquired infection has been variable and inconclusive for an associated risk of harm.[51] One of the first meta-analysis (11 studies, 127,000 patients) found a significant relationship between PPI use and *C difficile* infection, with an OR of 2.05 (95% CI, 1.47–2.85).[52] Further supporting the hypothesis of a direct causative association, a recent study found a significant dose response, with more aggressive acid suppression associated with higher ORs.[53] These findings also were supported by another meta-analysis (23 studies, 300,000 patients), which found PPI use was associated with an OR of 1.69 (95% CI, 1.395–1.974).[54] It is important to note that this study had several significant drawbacks including unaccountable heterogeneity and lack of information on potential confounders.

Despite the results of these earlier studies, the most recent studies offered conflicting viewpoints about the association between PPI use and increased risk of *C difficile* infection. In one study, researchers evaluated the association between acid-suppressing agents (PPIs and H2RAs) in 385 patients who had *C difficile* infection. Univariate analysis revealed both PPI and H2RA use was associated significantly with increased risk. After adjusting for age and comorbid conditions, however, there was no association with increased incidence or recurrence of *C difficile* infection.[55] Another case-controlled study in hospitalized patients found that length and dose of PPI exposure was not associated significantly with increased risk of *C difficile* infection ($P = .416$); rather, only antibiotic exposure in the past 3 months was associated significantly with *C difficile* infection (OR, 5.97; 95% CI, 2.40–14.8; $P = .001$).[56] Of note, the most recent review on detection, prevention, and treatment of *C difficile* did not include restriction or avoidance of PPIs in the recommendations for prevention of *C difficile* infection,[57] and this has not been recommended by multisociety clinical practice guidelines.[58]

Bottom line. To date, there is insufficient evidence to conclude that there is a definitive relationship between PPI use and *C difficile* infection. Given the increasing prevalence and morbidity associated with this infection, clinicians should be aware of this potential relationship, yet understand that confounding factors may play a significant role in the reported association. Appropriate use of PPIs should not be changed, however, until there is more conclusive evidence for potential harm.

Traveler's Diarrhea

Alterations of the gastric pH and possible related changes in susceptibility for enteric infections have been a topic of long-standing debate. Although gastric hypochlorhydria commonly is listed as a risk factor for traveler's diarrhea,[59] PPI exposure as a risk factor for enteric infections in travelers has not been studied formally. In fact, there is only one study that evaluated acid-reduction medication use and this study reported no significant association (OR, 6.9; range, 0.7–67.4) of traveler's diarrhea with antacids and H2-receptor–antagonist use.[60] A meta-analysis of the diagnosis of enteric infections did identify an increased risk of acute bacterial infection associated with the use of PPIs (OR, 3.33; 95% CI, 1.84–6.02).[52] A recent comprehensive analysis of the data on PPI use and enteric infections concluded that there was no association of PPI use and viral or parasitic enteric infections.[51]

Bottom line. The data on specific bacterial infections were overall supportive of no associated risk, albeit there were a few specific case reports suggesting a remote causal association. The International Society of Travel Medicine, however, does suggest discontinuing PPIs if traveling to areas with risk of enteric infection.[61] This seems reasonable if patient risk assessment is individualized and, when possible, PPIs can be stopped for a short period of time without other GI consequences.

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO), a condition that is associated with bloating, diarrhea, and malabsorption, recently has been associated with PPI use, although the significance of the association is uncertain.[53] In this report of 450 patients, SIBO was detected in 50% of patients using PPIs, 24.5% of patients with irritable bowel syndrome (IBS), and 6% of healthy control subjects. There was a statistically significant difference between patients using PPIs and those with IBS or healthy control subjects ($P < .001$).[62] The prevalence of SIBO increased after 1 year of treatment with PPI. This finding is supported by a smaller study of 42 patients, showing an association within the first 8 weeks of PPI use and also an increasing incidence of SIBO at the 6-month mark ($P < .05$).[63]

Since that article was published, 2 other retrospective case reviews have suggested no clear association between PPI use and SIBO. The first study, consisting of a database analysis of 675 patients who received a duodenal aspirate, found no clear association between SIBO and either PPI use or IBS ($P < .05$).[64] In addition, this study reported a positive association between older age (>50 y) and increased incidence of SIBO (OR, 5.7; 95% CI, 3.7–23.5). The second retrospective chart review of 1191 patients also found no association between PPI use and SIBO, using either univariate or multivariate regression.[65] In addition, treatment of SIBO is not impaired significantly in patients with PPI use because the reported eradication rate of SIBO (using rifaximin) was 87% in the PPI group and 91% in the IBS group.[62]

Bottom line. The relationship between PPI use and the development of SIBO is still not understood. Given the lack of randomized control trial data and reports that have significant confounding bias potentials, there are no clear supporting data at present to suggest a positive relationship.

Spontaneous Bacterial Peritonitis

Recent reports have suggested that there is a relationship between PPI use and the development of spontaneous bacterial peritonitis (SBP) in hospitalized cirrhotic patients with ascites. One study found a strong association (OR, 4.3; 95% CI, 1.3–11.7) between PPIs and SBP,[66] whereas another study found no significant association (OR, 1.0; 95% CI, 0.4–2.6).[67] A recent meta-analysis (4 studies, 772 patients) reported a significant association between PPI use and the development of SBP in cirrhotic patients (OR, 2.77; 95% CI, 1.82–4.23).[68] Given the large sample size compared with other studies on the topic and the low level of heterogeneity ($I^2 = 22\%$), the investigators recommended that PPIs should be used judiciously and only when clearly indicated for the cirrhotic patient.

A recent retrospective, propensity-matched cohort study used US Veterans Health Administration data to compare rates of serious infection associated with use of PPIs, H2RAs, or no

gastric acid suppressant in patients who began use after the development of decompensated cirrhosis. Serious infections were defined as any infection requiring hospitalization, and a subset of these infections were classified as related to acid suppression (pneumonia, bacteremia, *C difficile*, and SBP). A total of 4181 patients were included in the analysis (1905 PPI users, 248 H2RA users, and 2028 nonusers of gastric acid suppressants). Compared with nonusers, PPI users had a higher incidence of serious infections (adjusted hazard ratio, 1.66; 95% CI, 1.31–2.12) as well as acid-suppression–related infections (adjusted hazard ratio, 1.75; 95% CI, 1.32–2.34). These results are supportive of the previous findings that PPI use increases the risk for serious infections in patients with decompensated cirrhosis.[69] Recognizably, there is a background risk for patients with cirrhosis, in particular for patients with low protein ascites.[70] These patients have increased relative risks for disruptions in the composition of the GI microflora, owing to medical therapies and abnormal intestinal motility. Evidence suggests that 25% have small-bowel bacterial overgrowth, which can promote intestinal wall permeability that results in bacteria translocation and secondary infections (eg, SBP).

Bottom line. Although there is no definitive evidence for conclusion, PPI use in the cirrhotic patient should be scrutinized for appropriateness for use. In the studies to date suggesting possible causal harm, the majority of patients did not meet criteria to justify continued use of PPIs. At present, it would be premature to recommend routine discontinuance of PPIs in the patients who have appropriate indications for continued appropriately justified use of PPIs. The most recent data from Bajaj et al[66] suggest that H2RAs do not have this relative risk. Accordingly, if the patient has decompensated cirrhosis and needs continued acid-reduction therapy, it is reasonable to try switching to an H2RA and monitor the clinical effectiveness of the change in therapy.

Interstitial Nephritis

Several case reports have implicated PPIs as a cause of acute interstitial nephritis. This disorder is a humoral and cell-mediated hypersensitivity inflammatory reaction of the renal interstitium and tubules. A systematic review from 2007 found 64 cases documented in the literature, 12 of which were considered certainly associated, and 9 of which were probably associated.[71] Initial symptoms were nonspecific and included nausea, malaise, and fever. With such extensive use worldwide as the denominator, the investigators concluded that acute interstitial nephritis was a rare, idiosyncratic occurrence related to PPI use, but did not find enough evidence to support a causative relationship.

Bottom line. Despite the extreme rarity of the syndrome, the association cannot be dismissed and a high level of clinical suspicion to detect acute interstitial nephritis early in its course, especially soon after the initiation of PPI therapy, should be followed up.

Methotrexate

In December 2011 the FDA issued a cautionary warning for the use of high-dose methotrexate therapy in patients on PPIs, citing 2 cases in which delayed methotrexate metabolism was observed in patients who were undergoing induction dose therapy with 40 mg or more of methotrexate.[72] This delayed metabolism of methotrexate can lead to increased serum levels of methotrexate and its primary metabolite, 7-hydroxymethotrexate. The proposed mechanism for this delayed elimination involves PPI-mediated competitive inhibition of the breast cancer resistance protein (ATP-binding cassette, sub-family G, member 2 [ABCG2]), a low-affinity, high-capacity transporter of methotrexate.[73] One of the earliest studies on the coadministration of PPIs with methotrexate in 76 patients estimated that there was a 27% decrease in the clearance of methotrexate.[74] This association also was supported by a retrospective review of 171 methotrexate treatment cycles in 74 patients, which identified that coadministration of a PPI was a significant risk factor for delayed methotrexate elimination (OR, 2.65; 95% CI, 1.03–6.82); however, these researchers also performed an in vitro assessment showing that although there was an inhibitory effect of PPIs (omeprazole, lansoprazole, rabeprazole, and pantoprazole) on breast cancer resistance protein–mediated methotrexate transport, the effect occurred at levels 50 to 200 times higher than the usual therapeutic concentrations of PPIs.[75] This suggests that PPIs alone cannot fully explain the delayed elimination of methotrexate. Last, the most comprehensive review to date, which included data from the FDA's Adverse Event Reporting System, found that there were no reported incidences of methotrexate toxicity when an H2 blocker was substituted for the PPI.[76]

Bottom line. Coadministration of PPIs with high-dose methotrexate appears to be correlated with delayed methotrexate elimination and potentially may lead to methotrexate toxicity if not monitored appropriately. Given that there is no similarly reported interaction with H2 blockers, physicians should consider this switch before beginning induction doses of methotrexate therapy.

Conclusions

The reported associations for harm relative to PPI use 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 (eg, hypomagnesemia and interstitial nephritis). As such, these potential adverse effects should be not 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 justified to stop any therapy that may not be needed.

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Reprint requests

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Conflicts of interest

This author discloses the following: David Johnson is a consultant and clinical investigator for Takeda; a consultant for Pfizer; a clinical investigator for Astra Zeneca; and a clinical adjudicator for Esaii. The remaining author discloses no conflicts.