The Medical Letter®

on Drugs and Therapeutics

Volume 59 August 14, 2017

ISSUE No. 1527

IN THIS ISSUE

The Medical Letter®
on Drugs and Therapeutics

Volume 59 (Issue 1527) August 14, 2017

Take CME Exams

Safety of Long-Term PPI Use

Proton pump inhibitors (PPIs), which are used for treatment of gastroesophageal reflux disease (GERD) and for prevention of upper gastrointestinal adverse effects caused by NSAIDs and aspirin, are one of the most commonly prescribed classes of drugs in the US. All PPIs are similarly effective and generally well tolerated,[1,2] but their long-term use has been associated with a number of safety concerns.[3,4] Recommendations addressing these concerns have recently been published.[5,6]

FRACTURES — The labels of all prescription PPIs include a warning about an increased risk of fractures with long-term use.[7]

Mechanism – Reduced gastric acidity might interfere with calcium absorption.

Clinical Studies – A meta-analysis of 18 trials involving a total of 244,109 fracture cases found that PPI use was associated with a modest increase in the risk of hip (RR 1.26), spine (RR 1.58), and any-site fractures (RR 1.33). Fracture risk was similar with short-term (<1 year) and longer use.[8] A prospective cohort study that followed 9423 patients for 10 years found, after controlling for multiple risk factors, that PPI use was associated with a shorter time to a first nontraumatic fracture (HR 1.75).[9] However, a prospective cohort study including 79,899 postmenopausal women from the Nurses' Health Study found, after adjustment for confounding variables, no significant association between PPI use and fracture risk.[10] No association between PPI use and osteoporosis has been demonstrated.

HYPOMAGNESEMIA AND QT PROLONGATION — Hypomagnesemia has occurred rarely with prolonged PPI use and is usually accompanied by hypokalemia and hypocalcemia.[11] QT interval prolongation and torsades de pointes (TdP) associated with severe PPI-induced hypomagnesemia have been reported.[12-14] TdP has also been reported in patients taking a PPI concomitantly with drugs that directly prolong the QT interval.[15,16]

Mechanism – The exact mechanism by which PPIs cause hypomagnesemia is not known, but they may interfere with magnesium absorption.[17]

Table 1. Oral Proton Pump Inhibitors

Drug	Usual Adult Dosage[1,2]	Cost[3]
Dexlansoprazole – *Dexilant* (Takeda)	30-60 mg once/d	$258.70
Esomeprazole magnesium – generic	20-40 mg once/d	153.40
Nexium (AstraZeneca)		250.90
Nexium 24HR (OTC) (Pfizer)		17.90[4]
Lansoprazole – generic	15-30 mg once/d	56.50
Prevacid (Takeda)		415.10
Prevacid Solutab (Takeda)		415.10
Prevacid 24HR (OTC)[5] (GSK)		18.50[4]
Omeprazole – generic	20-40 mg once/d	11.80
Prilosec OTC[5] (AstraZeneca/P&G)		16.80[4]
Omeprazole/sodium bicarbonate[6] – generic	20-40 mg once/d	2620.90
Zegerid (Salix)		3033.80
Zegerid OTC[5] (Bayer)		16.10[4]
Pantoprazole – generic	40 mg once/d	6.00
Protonix (Pfizer)		393.30
Rabeprazole – generic	20 mg once/d	48.60
Aciphex (Eisai)		524.70
Aciphex Sprinkle (Eisai)		490.10[7]

OTC = over the counter

1. The lower end of the range is generally used for initial treatment of GERD. Higher or more frequent doses may be needed for patients with erosive esophagitis, peptic ulcer disease, hypersecretory conditions such as Zollinger-Ellison syndrome, or for treatment of *Helicobacter pylori* infection.
2. PPIs are generally taken 30-60 minutes before the first meal of the day. Taking one before the evening meal or taking the drug twice daily may be more effective for nocturnal acid control. PPIs should generally be swallowed whole and should not be crushed or chewed. Omeprazole/sodium bicarbonate *(Zegerid)* should be taken on an empty stomach at least 1 hour before a meal. Dexlansoprazole *(Dexilant)* can be taken with or without food.
3. Approximate WAC for 30 days' treatment with the lowest usual adult dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. July 5, 2017. Reprinted with permission by First Databank, Inc. All rights reserved. ©2017. www.fdbhealth.com/policies/drug-pricing-policy.
4. Approximate cost for 28 tablets or capsules.
5. Also available generically.
6. Immediate-release formulation that contains sodium bicarbonate as a buffer; it should be used with caution in patients on a low-sodium diet.
7. Approximate cost for 30 5-mg sprinkle capsules.

Clinical Studies – A meta-analysis of 9 observational trials including a total of 109,798 patients found that those who took a PPI had a higher risk (RR 1.43) of developing hypomagnesemia than those who did not.[18]

KIDNEY DISEASE — Use of PPIs has been associated rarely with acute interstitial nephritis and subsequent progression to chronic kidney disease (CKD).[19] Recent observational studies have reported an increased risk of CKD without acute kidney injury in long-term PPI users.

Mechanism – The mechanism by which PPIs might cause CKD is unknown.

Clinical Studies – A prospective cohort study in 10,482 patients with an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 m^2 who were followed for about 14 years found that the risk of CKD was higher (HR 1.45) in those who took a PPI than in those who did not.[20] A retrospective analysis of 114,833 new PPI and H2-receptor antagonist (H2RA) users found that patients taking a PPI were more likely to have a doubling of serum creatinine levels, a ≥30% decrease in eGFR, end-stage renal disease, and acute kidney injury than those taking an H2RA.[21] Another retrospective analysis of 144,032 PPI and H2RA users reported similar results, but found that <50% of cases of CKD were preceded by acute kidney injury.[22]

VITAMIN B12 DEFICIENCY — Decreased absorption and subsequent deficiency of vitamin B12 can occur with chronic use of PPIs and/or H2RAs, particularly with high doses and use in elderly patients.[23]

Mechanism – Release of vitamin B12 from dietary protein is dependent on gastric acid.

Clinical Studies – A case-control study compared use of a PPI or an H2RA to no acid-suppressing therapy in 25,956 patients with vitamin B12 deficiency and 184,199 controls. Patients who received ≥2 years' supply of a PPI or an H2RA had an increased risk of vitamin B12 deficiency. The risk appeared to be higher in women and younger patients.[24]

IRON DEFICIENCY — Use of PPIs can inhibit iron absorption, but the clinical significance of this effect is unclear.

Clinical Studies – A recent case-control study of 77,046 patients with newly diagnosed iron deficiency and 383,314 controls found that those taking a PPI or an H2RA for ≥2 years had an increased risk of iron deficiency; the risk was higher in those who took >1.5 PPI dosage units/day for at least 10 years.[25]

COMMUNITY-ACQUIRED PNEUMONIA (CAP) — Use of PPIs has been associated with a small increase in the risk of CAP, but the results of studies are conflicting.

Mechanism – The exact mechanism by which PPIs might increase the risk of CAP is not known. Reduced gastric acidity might promote bacterial colonization in the upper GI tract.

Clinical Studies – A meta-analysis of 9 trials involving a total of 120,863 pneumonia cases found that short-term PPI use (<30 days) or high-dose PPI therapy was associated with an increased risk of CAP.[26] However, a case-control review of 80,066 patients and 79,881 controls found, after adjustment for confounding factors, no significant association between PPI use and an increased risk of CAP.[27] A retrospective cohort study compared the incidence of hospitalization for CAP among new NSAID users who also started a PPI with those who did not take a PPI; after adjusting for confounding variables, there was no difference between the two groups in the 6-month incidence of CAP.[28]

CDI — Recent studies of an association between PPI use and an increased risk of *Clostridium difficile* infection (CDI) have produced conflicting results.

Mechanism – Whether acid suppression increases the risk of bacterial gastroenteritis and CDI is controversial. Reduced gastric acidity may promote bacterial colonization and increase the ability of *C. difficile* spores to convert to the vegetative form and survive in the lumen of the GI tract.

Clinical Studies – In a population-based study in 385 patients, use of PPIs and H2RAs appeared to be associated with an increased risk of CDI, but after adjusting for age and comorbid conditions, there was no association with an increased incidence or recurrence of the infection.[29] In a case-control study in 137 hospitalized patients, the duration or dose of PPI did not increase the risk of CDI.[30] In contrast, a pooled analysis of observational studies found that PPI use increased the risk of developing CDI by 75% and the risk of recurrent infection 2.5-fold.[31]

DEMENTIA — PPI use has been associated with cognitive decline, but a causal relationship has not been established and the evidence to date is limited.

Mechanism – PPIs can reduce vitamin B12 levels, which has been associated with cognitive decline.[32] Animal studies have found that PPI use can enhance beta-amyloid production in the brain.[33]

Clinical Studies – A prospective cohort study including 73,679 patients ≥75 years old without dementia who were followed for 7 years found that those who took a PPI regularly were more likely to develop dementia than those who did not (HR 1.44).[34]

A recently published analysis of prospectively collected data from 13,684 women in the Nurses' Health Study II did not find, after controlling for H2RA use, an association between PPI use and cognitive decline.[35]

ALL-CAUSE MORTALITY — An observational study in US veterans followed for >5 years found that,

compared to use of H2RAs, PPI use was associated with an increased risk of death (HR 1.25). The duration of PPI use and use in patients without an indication for a PPI were also associated with an increased risk of all-cause mortality.[36]

CONCLUSION — Long-term PPI use has been associated with an increasing number of safety concerns. Few of these concerns are supported by a causal relationship or consistent data. For patients with a clear indication for long-term treatment with a PPI, the benefits probably outweigh the risks. ■

1. Which PPI? Med Lett Drugs Ther 2015; 57:91.
2. Drugs for peptic ulcer disease and GERD. Treat Guidel Med Lett 2014; 12:25.
3. LH Eusebi et al. Proton pump inhibitors: risks of long-term use. J Gastroenterol Hepatol 2017; 32:1295.
4. MF Vaezi et al. Complications of proton pump inhibitor therapy. Gastroenterology 2017; 153:35.
5. B Farrell et al. Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. Can Fam Physician 2017; 63:354.
6. DE Freedberg et al. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gastroenterology 2017; 152:706.
7. PPIs and fracture risk. Med Lett Drugs Ther 2013; 55:15.
8. B Zhou et al. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016; 27:339.
9. LA Fraser et al. The effect of proton pump inhibitors on fracture risk: report from the Canadian Multicenter Osteoporosis Study. Osteoporos Int 2012 Aug 12 (epub).
10. H Khalili et al. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. BMJ 2012; 344:e372.
11. In brief: PPIs and hypomagnesemia. Med Lett Drugs Ther 2011; 53:25.
12. EJ Hoorn et al. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis 2010; 56:112.
13. BA Hansen and Ø Bruserud. Hypomagnesemia as a potentially life-threatening adverse effect of omeprazole. Oxf Med Case Reports 2016; 2016:147.
14. In brief: PPIs and torsades de pointes. Med Lett Drugs Ther 2016; 58:153.
15. H Asajima et al. Lansoprazole precipitated QT prolongation and torsade de pointes associated with disopyramide. Eur J Clin Pharmacol 2012; 68:331.
16. JN Bibawy et al. Pantoprazole (proton pump inhibitor) contributing to torsades de pointes storm. Circ Arrhythm Electrophysiol 2013; 6:e17.
17. JH William and J Danziger. Proton-pump inhibitor-induced hypomagnesemia: current research and proposed mechanisms. World J Nephrol 2016; 5:152.
18. W Cheungpasitporn et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail 2015; 37:1237.
19. T Antoniou et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open 2015; 3:e166.
20. B Lazarus et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med 2016; 176:238.
21. DCF Klatte et al. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. Gastroenterology 2017 June 2 (epub).
22. Y Xie et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int 2017; 91:1482.
23. L Linder et al. Drug-induced vitamin B12 deficiency: a focus on proton pump inhibitors and histamine-2 antagonists. J Pharm Pract 2016 Aug 12 (epub).
24. JR Lam et al. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA 2013; 310:2435.
25. JR Lam et al. Proton pump inhibitor and histamine 2 receptor antagonist use and iron deficiency. Gastroenterology 2017; 152:821.
26. C Giuliano et al. Are proton pump inhibitors associated with the development of community acquired pneumonia? A meta-analysis. Expert Rev Clin Pharmacol 2012; 5:337.
27. M Sarkar et al. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann Intern Med 2008; 149:391.
28. KB Filion et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. Gut 2014; 63:552.
29. S Khanna et al. Gastric acid suppression and outcomes in Clostridium difficile infection: a population-based study. Mayo Clin Proc 2012; 87:636.
30. AD Leonard et al. Proton pump inhibitors and diarrhoea related to Clostridium difficile infection in hospitalized patients: a case-controlled study. Intern Med J 2012; 42:591.
31. CS Kwok et al. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: a meta-analysis. Am J Gastroenterol 2012; 107:1011.
32. A Vogiatzoglou et al. Cognitive function in an elderly population: interaction between vitamin B12 status, depression, and apolipoprotein E ε4: the Hordaland Homocysteine Study. Psychosom Med 2013; 75:20.
33. N Badiola et al. The proton-pump inhibitor lansoprazole enhances amyloid beta production. PLoS One 2013; 8:e58837.
34. W Gomm et al. Association of proton pump inhibitors with the risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol 2016; 73:410.
35. P Lochhead et al. Association between proton pump inhibitor use and cognitive function in women. Gastroenterology 2017 July 18 (epub).
36. Y Xie et al. Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017; 7:e015735.

Subscription Services

Address:
The Medical Letter, Inc.
145 Huguenot St. Ste. 312
New Rochelle, NY 10801-7537
www.medicalletter.org

Customer Service:
Call: 800-211-2769 or 914-235-0500
Fax: 914-632-1733
E-mail: custserv@medicalletter.org

Permissions:
To reproduce any portion of this issue, please e-mail your request to:
permissions@medicalletter.org

Subscriptions (US):
1 year - $159; 2 years - $298;
3 years - $398. $65 per year
for students, interns, residents, and fellows in the US and Canada.
Reprints - $25/article; $35/issue

Site License Inquiries:
E-mail: SubQuote@medicalletter.org
Call: 800-211-2769
Special rates available for bulk subscriptions.

Get Connected:

 ISSN 1523-2859