

Our difficult break-up with proton pump inhibitors

A story from the front lines

A man in his 60s with a history of hypertension, diabetes mellitus 2 (A1C 7.3) and coronary artery disease was admitted from the emergency department for weakness and dizziness. He reported that for the last week, he felt dizzy upon standing and weakness and pain in his legs, leading to six falls. Workup revealed orthostatic hypotension, a magnesium of 1.2 and a calcium of 8.2. The patient had had one episode of diarrhea one week prior to admission but otherwise had no clear source for hypomagnesemia. Medication reconciliation showed that the patient was prescribed 40 mg of omeprazole daily and the patient confirmed that he had been taking this "forever." His earliest medication list in the electronic medical record was from 12 years prior and indeed did contain omeprazole at this dose. In the following 12 years, the patient had 29 primary care visits for management of his multiple comorbidities. The indication for omeprazole was not discussed, or listed in the problem list, at any visit. Additionally, endoscopy had not been performed. A magnesium level had never been checked previously.

During the present hospitalization, in addition to administering IV fluids and withholding his extensive anti-hypertensives to treat his orthostatic hypotension, the patient's magnesium was repleted, initially with IV magnesium and then PO, which was subsequently prescribed on discharge. The patient was reluctant to discontinue omeprazole, which he indicated was for heartburn that he was not longer experiencing. As such, ranitidine was started prior to discharge. Four days after discharge, at a post-hospitalization follow-up, the patient reported recurrence of heartburn and omeprazole was resumed at 40mg daily. His magnesium was still 1.2. He denied further falls.

A teachable moment

In 2011, the U.S. Food and Drug Administration (FDA) released a series of drug safety communications alerting providers and patients to the risk of hypomagnesemia in patients on long-term proton pump inhibitors (PPI) such as omeprazole.ⁱ Based on literature and patient safety reports, FDA reviewers determined that hypomagnesemia could occur after as little as three months of use, but was found most often in patients who had been on PPIs for greater than one year. Most patients who had full electrolyte panels had concurrent hypocalcemia, due to the negative effect that low magnesium has on parathyroid hormone secretion. They also reported cases of adverse events consistent with known effects of hypomagnesemia and hypocalcemia, including muscle spasm, seizures and arrhythmias. In about a quarter of cases, the hypomagnesemia did not resolve with magnesium supplementation alone, necessitating discontinuation of the PPI. In light of these findings, the FDA urged providers to consider monitoring magnesium levels in patients on PPIs.

The FDA's warning regarding the link between PPIs and hypomagnesemia was one of several safety concerns related to PPIs expressed by the organization between 2010 and 2012. Other concerns included increased risk of bone fractures and *Clostridium difficile*-associated diarrhea in patients on PPIs.ⁱⁱ Additional potential adverse effects of PPIs highlighted in a recent summary of systematic reviews on adverse effects of PPIs included acute and chronic kidney disease and pneumonia.ⁱⁱⁱ

In addition to the increasing awareness of the adverse effects of PPIs, the over-prescription of PPIs without appropriate clinical indication has also gained attention. Studies have shown that many patients are prescribed PPIs with absolutely no indication recorded.^{iv,v} Additionally, patients, particularly those with symptoms of gastro-esophageal reflux disease (GERD) such as our patient, are often inappropriately prescribed prolonged courses of PPIs. Guidelines published in the American Journal of Gastroenterology in 2013 indicate that convincing data for long-term PPI use in patients with GERD is limited to those with documented erosive esophagitis or Barrett's esophagus on upper endoscopy.^{vi} According to these guidelines, PPIs should only be administered in patients without these abnormalities if they have a recurrence of symptoms after they finish an 8 week course of a PPI. Additionally, efforts should be undertaken to determine the lowest effective dose (including potentially intermittent therapy). However, as with our patient, serial assessment of GERD symptoms and trials of cessation are rarely recorded.^{iv}

The potential side effects of long-term PPIs coupled with historic overprescribing should lead clinicians to critically examine whether the risk and benefit profile of PPIs in their patients remains favorable over the long-term, rather than blindly refilling prescriptions for years to decades without monitoring for benefit, assessing side effects, or attempting to lower the dose. However, perhaps given the traditional perception that PPIs are safe, clinicians may not prioritize this undertaking, especially in patients who have many competing comorbidities that require close monitoring and medication titration. Although in this case it was unclear whether the patient's subjective leg weakness and pain was indeed the result of hypomagnesemia given that his symptoms improved with treatment of his orthostatic hypotension, and an assessment of whether his hypomagnesemia was from an alternate etiology, such as urinary losses, was not performed, the fact that PPIs were so quickly resumed, despite ongoing significant hypomagnesemia and without an adequate trial of alternate GERD treatment, suggests that we are slow to challenge our biases even in the face of compelling evidence. However, without vigilance, we may unnecessarily perpetuate the harm of our predecessors who did not have the opportunity to benefit from the research we have today.

ⁱ Shepherd J. "FDA Drug Safety Podcast for Healthcare Professionals: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs)." U.S. Food and Drug Administration. March 2, 2011, last updated August 19, 2013. Accessed at <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm245455.htm> on February 3, 2016.

ⁱⁱ "Proton Pump Inhibitors Information" U.S. Food and Drug Administration.

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm213259.htm>

ⁱⁱⁱ Schoenfeld AJ and D Grady. Adverse Effects Associated With Proton Pump Inhibitors. *JAMA Intern Med.* 2016;176(2):172-174. doi:10.1001/jamainternmed.2015.7927.

^{iv} Patterson Burdsall D et al. Use of proton pump inhibitors with lack of diagnostic indications in 22 Midwestern US skilled nursing facilities. *J Am Med Dir Assoc.* 2013 Jun;14(6):429-32. doi: 10.1016/j.jamda.2013.01.021. Epub 2013 Apr 9.

^v Eid SM et al. Patterns and Predictors of Proton Pump Inhibitor Overuse among Academic and Non-Academic Hospitalists. *Intern Med* 49: 2561-2568, 2010.

doi:10.2169/internalmedicine.49.4064

^{vi} Katz PO, Gerson LB, and MF Vela. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am J Gastroenterol* 2013; 108:308–328; doi:10.1038/ajg.2012.444.