A Case of Severe Iron Deficiency Anemia Associated with Long-Term Proton Pump Inhibitor Use

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Abstract

The use of proton pump inhibitors (PPIs) in the treatment of gastrointestinal diseases has evolved over recent years. Initially intended for short-term use, PPIs are increasingly being used, often inappropriately, as long-term maintenance medications. The mechanism of action of PPIs is suppression of gastric basal and stimulated acid secretion by inhibiting the parietal cell H⁺/K⁺ ATP pump with a resultant increase in gastric pH and hypo- or achlorhydria. Although short-term use is related to few adverse effects, long-term use is associated with numerous complications. We present the case of a 58-year-old man with severe iron deficiency anemia due to malabsorption suspected to be caused by long-term PPI use. An extensive medical work up failed to reveal any definitive source of bleeding. An iron malabsorption test confirmed that iron was not being absorbed from the gastrointestinal tract. The Naranjo Adverse Drug Reaction Probability Scale and the Horn and Hansten Drug Interaction Probability Scale are suggestive of an association between long-term PPI use and the observed iron deficiency anemia. However, the patient’s death and lack of an autopsy prevented confirmatory follow-up data from being obtained to connect long-term PPI use as the culprit. Although there are currently no recommendations regarding screening for iron deficiency and/or anemia in patients on long-term PPI therapy, physicians should be aware of this potential side effect and consider monitoring in high-risk patients.

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Proton pump inhibitors (PPIs) are effective in the treatment of gastroesophageal reflux disease, erosive esophagitis, duodenal ulcers, and pathologic hypersecretory conditions. The use of PPIs has greatly increased in clinical practice over the past decade. The mechanism of action of PPIs is suppression of gastric basal and stimulated acid secretion by inhibiting the parietal cell H⁺/K⁺ ATP pump.¹ The result is an increase in gastric pH and hypo- or achlorhydria. Although initially intended for short-term use, PPIs are often inappropriately prescribed as a long-term maintenance medication.

PPIs cause few adverse effects with short-term use, whereas long-term use has come under scrutiny due to inappropriateness, drug-drug interactions, and the potential for adverse effects, most notably hip fractures, cardiac events, Clostridium difficile infection, pneumonia, and vitamin and mineral deficiencies. A review by Johnson and Oldfield² noted that the majority of adverse effects of PPIs are due to prolonged gastric acid suppression with long-term therapy.

Gastric acid plays a pivotal role in the absorption of iron. There are 2 types of dietary iron: (1) the heme type derived from animal blood and muscle and (2) the more common nonheme type derived from plants, fruits, vegetables, grains, and nuts. Accounting for ~10% of the Western diet, the heme type is absorbed independently of gastric pH, whereas the nonheme component requires an acidic pH for absorption.³ There are few case reports of iron deficiency induced by long-term omeprazole use and the effect of omeprazole on iron replacement therapy.³–⁵ In contrast, Koop and Bachem⁶ concluded that iron and ferritin malabsorption was unlikely to occur during the first 3 to 4 years of omeprazole therapy. However, Hutchinson et al⁷ found that long-term use of PPIs in hereditary hemochromatosis decreases iron absorption and limits the accumulation of iron in tissue stores.

Clinical case

A 58-year-old man with an extensive cardiac history including coronary artery disease, status post coronary artery bypass graft,
An extensive review of the patient's chart showed a normal complete blood count in February 2003. He was started on omeprazole during a clinic visit in September 2005 for indigestion symptoms and remained on PPI therapy through 2015. Since that time, his mean corpuscular volume (MCV) was microcytic and his red blood cell distribution width (RDW) was elevated. His hemoglobin continued to trend down, and he was first noted to be anemic in February 2012. In September 2013, iron studies were significant for a ferritin level of 5. (Table 1). He was treated with iron supplementation for years with good compliance, but never had significant improvement in iron studies or his anemia. He was fecal occult blood test negative on multiple occasions despite continued therapy with dual antiplatelet therapy as well. Of note, dual antiplatelet therapy was held as indicated in coronary artery disease with a recent non–ST-segment elevation myocardial infarction.

After a review of the literature regarding PPI use and its possible correlation with iron malabsorption, we determined that long-term PPI administration may have been a significant contributor to the patient's observed iron deficiency anemia. The patient was given intravenous iron supplementation while in the hospital and was discharged on ferrous sulfate 325-mg tablets to take twice daily, and his PPI was also discontinued. After discharge, the patient presented to an outside hospital in April 2015 and passed away before completion of outpatient follow-up lab testing. Although an autopsy was not performed on this patient, his cause of death was determined to be secondary to an acute myocardial infarction.

**Discussion**

This patient was diagnosed with iron deficiency anemia, without any definitive sources of bleeding identified after an extensive work-up including multiple EGDs, colonoscopies, a capsule endoscopy, CT scan, Meckel's scan, and numerous lab studies. Clinical evidence of iron malabsorption was confirmed following positive iron malabsorption testing. No other apparent causes of
malabsorption such as infectious, structural, or systemic were found. On review of his medications, omeprazole was the suspected culprit that could potentially be contributing to his malabsorption, as reported in some previously published clinical studies. If long-term PPI use was the origin of the patient’s profound anemia, the iron malabsorption was due to the alteration in gastric pH causing the body to be unable to absorb the majority of dietary iron. The Naranjo Adverse Drug Reaction Probability Scale and the Horn and Hansten Drug Interaction Probability Scale are both suggestive of an association between long-term PPI use and the observed iron deficiency anemia (scores of 5 and 6, respectively); however, the patient’s untimely death prevented confirmatory follow-up data from being obtained to confirm long-term PPI use as the culprit. Repeat lab work 3 months after cessation of omeprazole was planned to confirm recovery, as occurred in cases previously described.\(^3\),\(^5\)

The research investigating the relationship between PPI use and iron deficiency is not consistent. Tempel et al\(^8\) showed no effect on iron absorption with short-term PPI therapy. Some studies suggest that prolonged omeprazole use for at least 3 to 4 years is unlikely to cause iron and ferritin malabsorption,\(^6\) whereas Sarzynski et al\(^9\) found that among adults on long-term PPI therapy, defined as > 1 year, there was a significant decrease in hematologic indices from baseline.

Of note, our patient had no indication for long-term PPI therapy. He had mild reflux symptoms when therapy was initiated in 2005. Since that time, there was no mention of reflux in any subsequent documentation. He denied any further symptoms of heartburn or dysphagia. Such is likely the case with many patients; in their study, Sarzynski et al\(^9\) reported that 35% of patients on long-term PPI therapy had no indication for treatment.

PPIs have been used in clinical practice for ~25 years and have largely replaced histamine 2 receptor antagonists as first-line therapy. Furthermore, because many patients fail to make necessary lifestyle and dietary modifications, long-term medical therapy is required to alleviate symptoms. Long-term PPI therapy may lack benefit and may not be a benign treatment as once suspected because there are numerous adverse effects associated with this medication class.\(^1\),\(^2\)

This case emphasizes the need for improved awareness and future studies relating to the possible complications of long-term PPI use, including iron deficiency. More importantly, it is paramount that physicians routinely reassess the need for long-term medical therapy. Although there are no recommendations regarding screening for iron deficiency or anemia in patients on long-term PPI therapy, physicians and other health care professionals should be aware of this potential side effect and consider monitoring in high-risk patients.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

\[\text{1} \] Sheen E, Triadafilopoulous G. Adverse effects of long-term proton pump inhibitor therapy. \textit{Dig Dis Sci.} 2011;56:931–50.

\[\text{2} \] Johnson DA, Oldfield EC. Perspectives in Clinical Gastroenterology and Hepatology: Reported Side Effects and Complications of Long-term Proton Pump Inhibitor Use: Dissecting the Evidence. \textit{Clin Gastroenterol Hepatol.} 2013;11:458–464.

\[\text{3} \] Hashimoto R, Matsuda T, Chonan A. Iron-deficiency anemia cause by a proton pump inhibitor. \textit{Intern Med.} 2014;53:2297–9.

\[\text{4} \] Khatib MA, Rahim O, Kania R, Molloy P. Iron deficiency anemia: induced by long-term ingestion of omeprazole. \textit{Dig Dis Sci.} 2002;47:2596–7.

\[\text{5} \] Sharma VR, Brannon MA, Carloss EA. Effect of Omeprazole on Oral Iron Replacement in Patients with Iron Deficiency Anemia. \textit{Southern Medical Journal.} 2004;97:887–9.

\[\text{6} \] Koop H, Bachem MG. Serum iron, ferritin, and vitamin B12 during prolonged omeprazole therapy. \textit{J Clin Gastroenterol.} 1992;14:288–92.

\[\text{7} \] Hutchinson C, Geissler CA, Powell J, Bomford A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. \textit{Gut.} 2007;56:1291–5.

\[\text{8} \] Tempel M, Chawla A, Messina C, Celiker MY. Effects of omeprazole on iron absorption: preliminary study. \textit{Turk J Haematol.} 2013;30:307–10.

\[\text{9} \] Sarzynski E, Putterjarappa C, Xie Y, Grover M, Laird-Flick H. Association between Proton Pump Inhibitor Use and Anemia: A Retrospective Cohort Study. \textit{Dig Dis Sci.} 2011;56:2349–53.