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CASE REPORT

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Chronic use of PPIs as a potential cause of anemia: case reports and review of the literature

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Abstract

Proton pump inhibitors (PPIs) are drugs commonly used for many diseases of the gastrointestinal tract, such as gastroesophageal reflux disease, erosive esophagitis, and peptic ulcers of the stomach and duodenum. Used for about 30 years, they are currently the most effective drugs that reduce the gastric secretion of hydrochloric acid. However, a dramatic increase in their consumption has been recently observed. Very often, they are used not in accordance with the guidelines. The consequences of the long-term use of PPIs may be various, with the most common side effects being bone fractures, cardiovascular events, recurrent infections, and vitamin and mineral deficiencies. Case report: An 82-year-old and a 58-year-old patients who had been taking omeprazole, a PPI for several years, developed vitamin B12 and iron deficiency anemia. Both patients were administered PPI orally for nonspecific dyspeptic symptoms. An evaluation of the gastrointestinal tract did not reveal the evident causes of gastrointestinal blood loss. They were also screened negative for *Helicobacter pylori* infection. Conclusions: There are no definitive pieces of evidence that the long-term use of PPIs can induce anemia, but our cases strongly suggest this thesis. Physicians should be aware of this potential side effect and consider monitoring in high-risk patients.

Keywords:
PPIs, anemia, iron deficiency, B12 deficiency

Introduction

Proton pump inhibitors (PPIs) are irreplaceable in the treatment of many common diseases of the gastrointestinal tract, such as gastroesophageal reflux disease (GERD), erosive esophagitis, and peptic ulcers of the stomach and duodenum. The main mechanism of their action is the inhibition of ATPase K^+/H^+ (proton pump), which leads to a reduction of the number of hydrogen ions released into the stomach and results in decreased production of gastric acid, increased pH, and hypo- or achlorhydria. In medicine, PPIs have been used for about 30 years. Recently, a drastic increase in their consumption has been observed. Relatively low price, high efficiency, and wide availability (over-the-counter (OTC) drugs) lead to their increased usage but not in accordance with the applicable guidelines, for example in prophylaxis of stress ulcer in patients with low risk of bleeding, either in combination with many other pharmaceuticals as "gastroprotective" drugs or with the treatment of nonspecific abdominal symptoms. It has been estimated that PPIs were prescribed 119 million times in the United States in 2009 and that patients spend over 24 billion dollars a year globally [1, 2]. The number of reports of the danger that might be caused by the long-term use of these drugs is still rising [2, 3, 4]. The most common side effects include bone fractures, cardiovascular events, recurrent infections, as well as vitamin and mineral deficiencies. Small intestinal bacterial overgrowth (SIBO) frequency is also probably increased by PPIs administration. Presumably, SIBO is closely related to dysbiosis [5, 6]. This article seeks to address a possible link between prolonged PPIs intake and vitamin B12 and iron deficiency anemia and uses two case reports to support this thesis.

Case report

Case 1

An 82-year-old male was admitted to the Hematology Department for diagnostics toward mild hemolytic anemia. He reported severe weakness, apathy, drowsiness, and recurrent dizziness. So far, he had been treated for advanced osteoarthritis of the knee joints. For several years, he had been regularly taking nonsteroidal anti-inflammatory drugs (NSAIDs) in high doses (ibuprofen 400–600 mg/per day and diclofenac about 200 mg/per day) and PPI (omeprazole 20 mg/per day), which were supposed to protect the gastrointestinal mucosa. Laboratory studies showed that there was a decreased hemoglobin (Hgb) level of 12.6 g/dl (a normal range: 13.7–17.5 g/dl), macrocytosis – mean corpuscular volume (MCV) – 112 fl (a normal range: 79–92 fl), prolonged red cell distribution width – standard deviation (RDW-SD) – 60.04 fl, increased reticulocyte percentage (3.99%), and increased hemolysis index: low concentration haptoglobin (0.14 g/l), elevated total bilirubin (2.2 mg/dl) with domination of indirect bilirubin, and high lactate dehydrogenase (LDH) – 650 IU/l. There was a significantly lowered vitamin B12 concentration

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in serum (121.2 pg/ml, a normal range: 191–663 pg/ml). The iron level was normal (109.8 µg/dl, a normal range: 59–158 µg/dl). An evaluation of the gastrointestinal tract did not reveal the presence of *Helicobacter pylori* antigen or blood in the stool. Anti-parietal cell antibodies (APCAs) were not detected. The control ultrasound scan of the abdomen showed only the presence of a gallstone with a size of several millimeters in the gallbladder. The Coombs test was performed and no antibodies against red blood cells (RBCs) surface antigens were detected. The patient did not agree to the endoscopic examinations. The patient received treatment with parenteral supplementation of vitamin B12 in a starting dose of 1,000 µg intramuscularly once a day for a week, then once a week for 1 month, and then once a month. The PPI was discontinued and analgesia was modified. Drugs from the NSAIDs group were switched to low-dose opioids, buprenorphine in transdermal patches. The applied treatment improved the condition of the patient, caused the disappearance of clinical symptoms, and the stabilization of blood count parameters – Hgb (15.6 g/dl), MCV (94.1 fl), and vitamin B12 (530 pg/ml), as well as an appropriate control of the pain associated with arthrosis of the knee joints.

Case 2

A 58-year-old male was consulted in Hematologic Outpatient Department for mild normocytic anemia (Hgb 11.9 g/dl, MCV 85.4 fl), which had been observed for about a year. He had numerous chronic diseases such as recurrent atrial fibrillation, paroxysmal left bundle branch block (LBBB), arterial hypertension, New York Heart Association (NYHA) class II heart failure, cardiomyopathy, and type II diabetes (requiring insulin therapy). Moreover, the patient suffered from recurrent bacterial pneumonia and triple exudative pericarditis during the last 2 years, which resulted in hospitalization at the intensive care unit (ICU). The cause of pericarditis was unclear but due to the fast progression of the disease and continuous anticoagulation therapy, the pericardial puncture was abandoned. The treatment based on NSAIDs and colchicine resulted in the reduction of the symptoms after a couple of weeks. During the first hematologic consultation, the patient complained of significant weakness, lack of tolerance of physical activity,

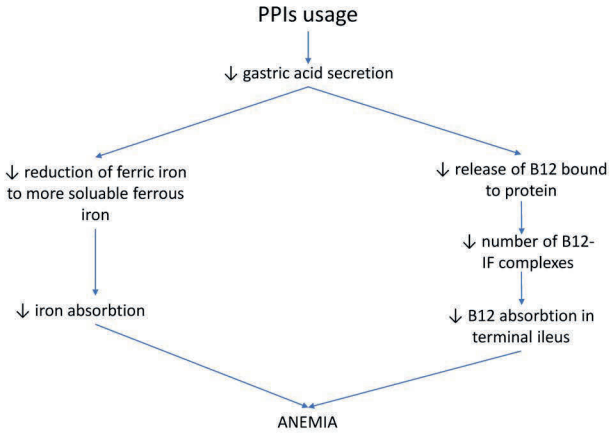

Fig. 1. Mechanism of anemia in chronic PPIs usage

concentration disorders, and sexual dysfunction. He has been taking cardiovascular medicines (propafenone, metoprolol, and atorvastatin) regularly for several years as well as antihypertensive (amlodipine, torasemide, telmisartan, ramipril, captopril, and nitrendipine) and antidiabetic drugs (metformin), anticoagulants (dabigatran), and the PPI (pantoprazole) as a "protection" of the stomach mucosa. The basic laboratory tests revealed a complex iron (22 µg/dl, a normal range: 59–198 µg/dl), ferritin (13 µg/l, a normal range: 30–400 µg/l), and vitamin B12 (182 pg/ml, a normal range: 191–663 pg/ml) deficiency. The gastrointestinal tract endoscopy did not reveal any gross abnormalities, and the fecal occult blood (FOB) was negative. Furthermore, the iron absorption curve did not present any satisfactory increase in the iron concentration. The baseline serum iron concentration was 34 µg/dl, after 2 h – 51 µg/dl, after 4 h – 61 µg/dl. It was recommended that PPIs should be discontinued. The treatment included a cycle of intramuscular injections of vitamin B12 and iron oral supplementation. In control tests performed after 1 month of the treatment, there was an increase in Hgb level to 14.6 g/dl, improvement in laboratory indicators of iron metabolism – iron (94 µg/dl), ferritin (27 µg/l), and increase in concentration of vitamin B12 (490 pg/ml) in serum. Two months after the PPI discontinuation and the initiation of the treatment, Hgb level achieved 15.1 g/dl. Above all, the patient reported a significant improvement in well-being and resolution of symptoms.

Discussion

The relationship between PPIs and vitamin B12

Low pH in the stomach is necessary at the early stages of vitamin B12 absorption. So, suppression of gastric acid secretion by PPIs may result in impaired absorption and B12 (cobalamin) deficiency [8]. The acidic environment and the presence of pepsin allow the release of vitamin B12 from binding to the protein. Then, free molecules of cobalamin are binding to the R protein secreted by salivary and parietal cells. The B12-R protein complex is then transported to the duodenum, where it will be broken down by pancreatic enzymes. In the next step, free B12 is bound to the internal factor (IF) produced by the parietal cells. Eventually, the IF-B12 complex is absorbed in the terminal ileum [7].

Clinical observations on the impact of taking PPI-type drugs on the B12 absorption processes may be contradictory [7]. Jensen et al. in a study conducted in a group of patients taking PPIs in low doses or for a short period of time did not show a reduction in the level of B12 [7, 9]. Similar conclusions were made by Schenk et al. in the group of patients taking long-term PPIs (from 3 to 7 years), and they did not show statistically significant differences regarding vitamin B12 concentrations before and after the treatment [10, 11].

However, in a study conducted at Kaiser Permanente in Northern California, which included an impressive group of subjects – 25,696 patients and 184,199 healthy subjects, there was an increased risk of vitamin B12 deficiency (OR = 1.65; 95% CI = 1.58–1.73) among patients taking PPIs for 2 years and longer [12]. In another study comparing the influence of a short-term (<12 months) and long-term (± 12 months) use of PPI and H2RA on the risk of vitamin B12 deficiency, the risk was significantly higher in patients from the second

group (OR = 4.46; 95% CI = 1.49–13.33) [13]. In a retrospective analysis, Force et al. showed that patients requiring parenteral vitamin B12 supplementation in the treatment of megaloblastic anemia were statistically more likely to have an earlier history of taking PPI-type medicines for at least 10 months [14].

Maes et al. [15] in their review of the side effects of PPIs, argue that many pieces of evidence points to an association between PPIs and vitamin B12 deficiency, and contradictory data from other reports may be caused by a too small group of patients, a too high threshold for vitamin B12 deficiency and a wide variety of accompanying diseases. A meta-analysis of many studies has shown that the risk of vitamin B12 deficiency associated with the use of gastric acid-suppressive therapy is around 80%. The control of vitamin B12 level in patients taking PPIs chronically seems to have a strong justification.

The patient presented in the first case had been taking PPIs for many years and presented megaloblastic anemia with a lowered level of B12 vitamin. Withdrawal of omeprazole resulted in a very quick replenishment of B12 reserves during supplementary therapy.

Relationship between PPIs and iron deficiency

Iron in the diet occurs in a free form or bound with heme. Gastric acid facilitates the absorption of iron unbound to heme by reducing iron to a more soluble form [16]. The clinical experience associated with PPIs and secondary iron deficiency varies.

Tempel et al. [17] showed no effect on iron absorption during short-term PPI therapy. Koop et al. [18] also suggest that the prolonged use of omeprazole for at least 3–4 years probably will not result in poor absorption of iron and ferritin. Other conclusions were presented by Sarzyński et al. [19] who noted a significant decrease in blood counts compared to baseline values in the adult group of long-term PPIs users (>1 year) [19]. In one recent study, Tran-Duy et al. [20] showed that PPI therapy for at least 1 year significantly increases the risk of iron deficiency. Researchers using the UK Clinical Practice Research Datalink (CPRD) database identified a group of 26,806 iron-deficient patients diagnosed in 2005–2015 and compared them with the same randomly selected control group. The adjusted risk ratio of iron deficiency among patients receiving PPIs compared to those not taking PPIs was 3.60 (95% CI 3.32–3.91) and 1.51 (95% CI 1.44–1.58).

In the literature, there are single descriptions of clinical cases of patients with iron deficiency anemia in the course of PPI therapy. Clinical observations can also be found that discontinuation of PPIs was sufficient to improve the erythrocytic parameters [21, 22, 23]. In our second presented case, patient taking PPIs regularly for many years had a very low iron concentration and initial oral iron supplementation had no clinical effect. Similarly, the results of the iron absorption curve were unsatisfactory. Only after the discontinuation of PPIs, the serum iron and Hgb levels were improved.

Conclusions

On the basis of almost 30 years of experience in PPIs use, it should be noted that drugs from this group are one of the most effective pharmacological methods for reducing the pH in the stomach, and thus have an excellent safety profile. However, the prolonged and often completely inappropriate use of PPIs without clinical indications is a large clinical problem in recent years, which, as shown by many studies and our observations, raises concerns about numerous short- and long-term side-effects.

Authors' contributions

MP – was a major contributor in writing the manuscript. ASS, MM, KK – participated in the collection of data and data interpretation. MM, MH – contributed to the data analysis and interpretation. ASS – critically revised the manuscript. All authors – contributed to writing and review of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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