International Journal of Basic & Clinical Pharmacology
Kumar SS et al. Int J Basic Clin Pharmacol. 2023 Nov;12(6):864-869
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20233200

Case Report

A case study of an adverse drug reaction caused by long term use of proton pump inhibitors

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Received: 27 July 2023
Revised: 28 August 2023
Accepted: 31 August 2023

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ABSTRACT

Proton pump inhibitors (PPI) are the class of drugs used to treat a wide variety of disorders related to the stomach's acid production. Although it is considered safe for short term use, reports revealed that many serious life-threatening adverse reactions occurred from long term use. Here we report a case of hypomagnesemia and hypocalcemia induced by long-term use of PPIs in a patient with crest syndrome. From his past history, it was revealed that he was on pantoprazole 40 mg for more than 3 months. While he was admitted here for other complaints, we were able to discover that he had hypomagnesemia defined by low magnesium level of 1.3 mg/dL. As a consequence, he also showed signs of hypocalcemia with a low calcium level of 7 mg/dL. A peculiar complaint seen in this patient was three episodes of supraventricular tachycardia which is the most common cardiac manifestations of hypomagnesemia. As a conclusion, hypomagnesemia can sometimes be asymptomatic and cause unspecific and serious manifestations such as asthenia, paresthesia's, seizures, arrhythmias, and cardiac arrest. Hence routine monitoring of serum magnesium and calcium levels should be made mandatory in practice for patients on long term use of PPI. Besides, it should be kept in mind that interchanging PPI class with histamine 2 receptor antagonist or fitful use of PPI may not cause hypomagnesemia.

Keywords: Hypomagnesemia, Hypocalcemia, Supraventricular tachycardia, PPI, Histamine 2 receptor antagonist

INTRODUCTION

Proton pump inhibitors (PPI) are the drugs that have a prolonged and profound action on the cells lining the stomach resulting in decreased acid production.[1] PPIs are the most prevailing drugs used extensively in the primary care setting. A number of PPIs are granted approval by the U.S. food and drug administration for the following disease conditions such as *H. pylori* infections, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), erosive esophagitis, Zollinger Ellison syndrome and also plays a role in the prophylactic treatment of stress induced ulcers, gastrointestinal risks in patients receiving anticoagulants and in those suspected to have NSAID induced ulcer complications.[2] PPIs work by blocking the gastric H, $K^{-ATPase}$ in the gastric parietal cells of the stomach which results in suppression of acid secretion. Over the past several decades, numerous studies have revealed that PPIs are used extravagantly and unseemly in patient care.[1] In common, PPIs are well tolerated and safe with the most frequently reported minor side effects of short-term use such as gastrointestinal symptoms including nausea, abdominal, pain, diarrhea, constipation, flatulence, headache, rash, and dizziness. Even though it is considered safe for short term use, reports revealed that many serious life-threatening adverse

reactions occurred from long term use.[3] As esophageal dysmotility is more predominantly seen in systemic sclerosis patients, the use of PPIs are also increasing parallelly.[4] It is more obvious from the recent studies that prolonged gastroesophageal reflux leading to chronic GERD is highly prevalent in systemic sclerosis and exposes the patients to PPIs over a long period. 40-70% of systemic sclerosis patients experience small bowel movement which is associated with bacterial growth leading to malabsorption showing that GI complications are more common in systemic sclerosis.[5] Studies have shown that 50% of systemic sclerosis patients experience clinically significant and symptomatic GI involvement. Magnesium plays a crucial role as a cation being implicated in many biochemical and physiological processes in our bodies. Decreased magnesium levels cause tetany, cardiac arrhythmias, convulsions, hypocalcemia, and hypokalemia. Hypomagnesemia impairs magnesium-dependent adenyl cyclase generation of cyclic adenosine monophosphate (cAMP) leading to decreased parathyroid hormone release (PTH). As calcium levels are regulated by PTH, decreased PTH release leads to hypocalcemia.[6] US FDA stated and released a safety announcement that long term use of proton pump inhibitor causes hypomagnesemia and hypocalcemia. The Australian therapeutic goods administration (TGA) declared a similar caution in June 2011.[7]

CASE REPORT

In the department of internal medicine, a 64-year-old male was admitted with complaint of swelling and redness in the scrotum for two days, as well as a history of a self-fall at home resulting in a fractured right hip 10 days ago. The patient was operated on in another hospital before being admitted here. There was a history of type 2 DM, systemic hypertension for 5 years, chronic liver disease, and osteoarthritis in the right knee. According to his past medication history, he has been taking pantoprazole 40 mg for at least three months.

The patient arrived at the hospital drowsy and afebrile. On physical examination, he was pale and had signs of edema. Systemic examination revealed a positive crepitus of the respiratory tract and a soft and distended abdomen.

Further investigations were performed to make a definitive diagnosis: Serum antinuclear antibodies were positive (3+) and ENA profile showed a CREST syndrome, whereupon steroids were administered. Peripheral smear examination showed marked neutrophilia and marked anemia. CT Chest examination revealed interstitial lung disease. LFT revealed hypoalbuminemia, for which a transfusion of 2 units of packed red blood cells was performed. In addition, his complete blood count revealed thrombocytopenia (78000/uL) and electrolyte levels showed hypokalemia (3.1 mmol/L), for which he received KCl syrup (10 ml) BD. His laboratory tests revealed hypomagnesemia and hypocalcemia with values of 1.3 and 7.0 mg/dl, respectively. He was treated with 1 gram of magnesium to prevent further complications and vitamin C to increase calcium absorption. The magnesium level was slowly increased and reached 1.9 mg/dl before he was discharged.

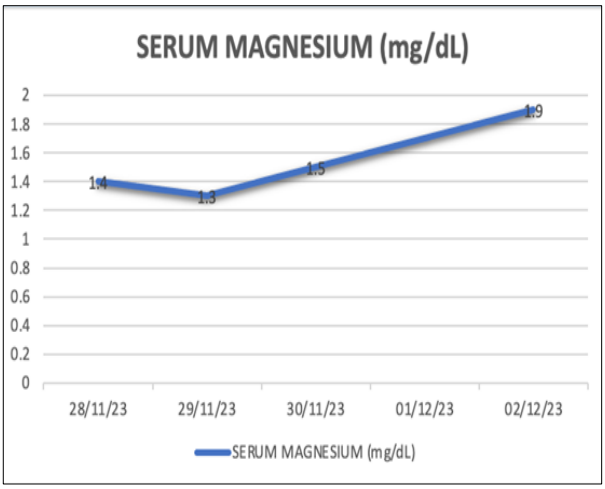

Figure 1: Course of the patient's magnesium levels.

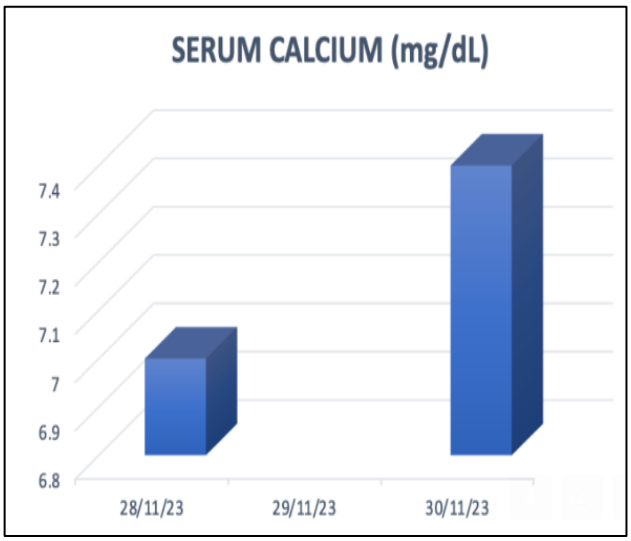

Figure 2: Course of the patient's calcium levels.

This patient experienced three episodes of supraventricular tachycardia during hospitalization, which is one of the most common cardiac manifestations of hypomagnesemia, including ventricular tachycardia, supraventricular tachycardia, and atrial fibrillation. The patient treated supraventricular tachycardia with adenosine injection of 6 mg and verapamil as maintenance therapy.

Because of signs of bilateral leg swelling, a venous Doppler examination was ordered, which revealed no evidence of deep venous thrombosis. Due to complaints of pain in the right thigh and knee, a CT-examination of the abdomen with thigh was ordered. This revealed loss of volume of the posterior segments of the right liver lobe with hypertrophy of the caudate lobe and fissure widening-possibly early liver parenchymal disease-diffuse scrotal wall edema, and an active contrast leak/pseudoaneurysm

with a large intramuscular hematoma in the vastus muscle compartment of the right thigh, as described. A right lower extremity angiogram and embolization were suggested, and 2 units of fresh frozen plasma (FFP) were administered. After the procedure, he was unremarkable. The patient was treated with IV. After the procedure, he was uneventful. The patient was treated with IV fluid, IV antibiotics, steroids, antipyretics, antiemetics, PPI and other supportive measures. His symptoms improved and his condition was good and afebrile. Therefore, his discharge was planned.

DISCUSSION

Following potassium, magnesium is the second most dominant intracellular cation.[8] It is of paramount importance in many reactions that occur in the human body such as energy metabolism as it forms a key complex with ATP in all enzymatic reactions involving ATP.[9] The daily requirement of magnesium is between 200-300 mg or 4.5 mg/kg/day, however only 1/3 of this amount is absorbed through the small intestine. Urinary magnesium excretion is approximately 100 mg/day (4 mmol/day). The normal reference value of serum magnesium is between 1.82 to 2.30 mg/dL (0.75-0.95 mmol/L).[10] Hypomagnesemia defined as serum magnesium levels less than 1.6 or 0.66 mmol/L may affect almost every organ system despite being chronic or subtle. Clinically significant signs and symptoms attributable to hypomagnesemia does not arise until serum magnesium levels fall below 1.2 mg/dL (0.5 mmol/L).[9] Hypomagnesemia can sometimes be asymptomatic and cause unspecific and serious manifestations such as asthenia, paresthesia, seizures, arrhythmias, and cardiac arrest.[11] Hypocalcemia can sometimes follow hypomagnesemia.[12]

Mechanisms of proton pump inhibitor-induced hypomagnesemia

Hypomagnesemia caused as a result of PPI use was first proclaimed in the year 2006.[13] Thenceforth, multiple clinical studies have affirmed that PPI use can lead to hypomagnesemia. Furthermore, as studies have disclosed that PPI users showing mild hypomagnesemia (± 0.6 mmol/L) can be asymptomatic, it is ubiquitous to miss this diagnosis as routine measurements of Mg2+ are not performed in practice.[14]

PPIs affect paracellular transport of Mg2+ in the small intestine

The mechanism of Mg2+ absorption in the small intestine through enterocytes into the bloodstream shows a dual kinetic process that includes two main mechanisms: an active transcellular pathway (saturable) and a passive paracellular pathway (non-saturable). Two factors are considered significant here: Magnesium availability and tight junction permeability which are jeopardized by the long-term use of PPIs.[15]

Luminal pH of the small intestine

PPIs influence the luminal pH of the parts of small intestine thereby increasing the pH. This causes a reduction in the magnesium solubility and subsequently absorption.[15]

TRPM6 function

The pH in the colon may also regulates the activity TRPM6/7, which shows the luminal Mg2+ channel in the colon.[16] Considering that TRPM6 activity is higher at acidic pH, the PPIs-induced increase in colonic pH might reduce TRPM6-mediated Mg2+ absorption.[15] Another likelihood is that the passive paracellular transport mechanism is much less efficient. Evenpoel demonstrated that PPIs can increase the inward intestinal permeability to sucrose, proposing that the function of the tight junction barrier that regulates paracellular transport can be affected by PPIs. However, that hypothesis remains unproven.

Gut microbiome

Gut microbiome plays a vital role in mg2+ solubility and absorption in our body. Bacterial fermentation in the colon decreases the pH levels and aids in solubility and absorption of magnesium but on the contrary, studies have shown that long term proton pump use can lower gut microbial diversity and change its gut microbiome composition.[17-21] Magnesium transport in the colon is primarily mediated by ion channels i.e TRPM6 AND TRPM7 and its decline in activity is the sole reason for PPI related hypomagnesemia.[22] Recent studies have shown that low gut microbiota diversity and reduced magnesium intake can influence hypomagnesemia in PPI user. Mutations of genes which is mainly implicated in distal magnesium reabsorption process are the reason behind the low-grade renal magnesium leak. [23]

Treatment of PPI induced hypomagnesemia and hypocalcemia

The main therapy includes discontinuation of proton pump inhibitor, calcium and magnesium supplementation.[24] In this case, patient was treated with 1gm of IV magnesium and vitamin C to increase calcium absorption. Clinicians must know about these serious adverse effects to avoid potentially life threatening complications and events.[25] The reason behind ppi induced hypomagnesemia being reduced magnesium intake, reduced absorption and malabsorption due to underlying intestinal disturbances should have been ruled out before initiating PPI therapy.[26]

On the other side, patients who are at high risk of developing complications like cardiac arrhythmias should be identified immediately and should be switched to a H2 receptor antagonist like cimetidine or ranitidine Also, other drugs which decreases magnesium levels should be noted before initiating a PPI therapy.[25] For patients who require ppi therapy regardless of hypomagnesemia, an

oral magnesium supplementation will balance out the serum magnesium levels by enhancing the intestinal absorption.[27,28]

Hypomagnesemia and SVT

One of the most recognized and serious complication of long-term PPI therapy is cardiac arrhythmias which can evolve immediately after long term asymptomatic interval. Magnesium is one of the cofactors of the membrane Na-K pump; it regulates the potassium movement in the cell.[29] Magnesium deficiency can reduce the pump's activity and decline the intracellular movement of potassium into the cell. These changes results in partial depolarization which results in disruption of resting membrane potential of cardiac cells and aggregate cardiac arrhythmias.[30] Beluri et al in a study figured out that the possibility of ventricular arrhythmias in magnesium deficiency increased significantly and indicates that hypomagnesemia is one of the salient causes of ventricular arrhythmias which are clinically correlated in our patient.[31]

PPI induced hypocalcemia

Dietary Calcium in our body is absorbed mainly through paracellular and transcellular pathway through vanilloid 6 channel at duodenum, and proximal jejunum.[32,33] Their absorption is dramatically reduced in achlorhydria, associating PPIs as a causative agent for calcium malabsorption.[34] The mechanism behind this is typically due to the blocking of H+K+ATPase of parietal cells in the stomach by PPIs.[35] As calcium absorption is a pH dependent process, the above mechanism decreases the bioavailability of calcium.

On the other hand, the phenomenon of hypocalcemia can be more of a secondary calcium imbalance that results from hypomagnesemia. This is attributed to the functional hypothyroidism as parathyroid hormone is a magnesium dependent process. The hypocalcemia is referred as secondary because it results as a repercussion of hypomagnesemia.

In our patient, various other donating factors towards hypocalcemia are evident. Of which hypoalbuminemia as seen in this case is theoretically well known that decreased amount of albumin leads to decreased calcium binding thereby causing a decline in the total calcium levels. In comorbid conditions like diabetes mellitus (DM), deviation of calcium homeostasis is multifactorial. Recent studies have revealed a correlation between calcium homeostasis and development of DM. Apart from calcium regulating hormones, diabetes mellitus also influences the calcium regulating organs which impede the intestinal calcium absorption, decelerate bone elongation and renal calcium wasting. The decrease in calcium absorption usually resolves to the control level by giving insulin.

So mayhap, PPI induced hypocalcemia is unconventionally an indirect mechanism rather than a direct mechanism.

CONCLUSION

From various cases reported on PPI induced hypomagnesemia and hypocalcemia, majority of them were caused by Omeprazole and esomeprazole. Although a higher incidence was seen with omeprazole as reported by authors Cundy et al, Epstein et al, Hoorn et al, Fernández et al and Shabajee et al. However, it is known that PPI - associated hypomagnesemia and hypocalcemia is not a distinctive characteristic of the drug rather it is confined to the entire PPI. As this is a class effect, swapping with an alternative PPI resulted in electrolyte imbalance. Intriguingly, in our patient pantoprazole which is a less potent drug has however resulted in hypomagnesemia and hypocalcemia. Hypomagnesemia in patients who are treated with PPI for the long term are very rare but it may be life threatening. Hypomagnesemia secondary to long term consumption of PPI have been underdiagnosed due to lack of knowledge and less frequency of blood magnesium level monitoring in routine. As adverse effects can be asymptomatic most of the times, monitoring blood magnesium and calcium levels should be made mandatory for patients managed with long term use of PPI and symptoms like asthenia and generalized paresthesia should not be neglected and meticulously reported on time. Thus, in an era of massive use of PPI, if the need for these agents is critical in patients, histamine 2 receptor antagonist can be substituted, or fitful use of PPIs might not cause hypomagnesemia.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kumar S, Ravindran S, Philips ML, Ganesh SB. A case study of an adverse drug reaction caused by long term use of proton pump inhibitors. Int J Basic Clin Pharmacol 2023;12:864-9.