The hidden danger of proton pump inhibitor: A case of hypomagnesemia

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SUMMARY

Hypomagnesemia has increasingly been reported as a side effect of prolonged use of proton pump inhibitors (PPI) over the years. It is a potentially serious but often under recognised complication. We present a case of a 75-year-old man who presented with bilateral upper and lower limb numbness. Laboratory evaluation revealed hypomagnesemia, hypokalaemia and hypocalcaemia, which was ultimately attributed to long-term use of a proton pump inhibitor. After discontinuation of the PPI, magnesium levels normalised, and the patient's symptoms resolved. There was also a clear causal relationship found between PPI rechallenge and recurrent hypomagnesemia throughout time. This case highlights the importance of recognising hypomagnesemia as a clinically significant side effect of long-term PPI usage. Dosage and duration of PPI should be reviewed regularly to assess the need for continuation to prevent unfavourable side effects.

INTRODUCTION

Proton pump inhibitors are widely prescribed for the treatment and prevention of gastroesophageal reflux, peptic ulcer, gastritis and esophagitis. With rising PPI use, adverse effects like hypomagnesemia, organ damage, infections, and nutrient malabsorption are increasingly reported.[1] Although rare, proton pump inhibitor-induced hypomagnesemia (PPIH) is a clinically significant complication of prolonged PPI use. Hypomagnesemia can lead to neuromuscular complications, cardiac arrhythmia and other electrolyte disturbances. Withdrawal of PPI is the most effective approach to resolving hypomagnesemia in affected patients. Numerous studies have reported on the overutilisation of PPI worldwide. A local study by Far et al., demonstrated that 46% of patients were inappropriately prescribed PPI.[2] Through this case, we aim to emphasise the importance of recognising PPI-induced hypomagnesemia and the need for regular review of the indication of long-term PPI usage.

CASE PRESENTATION

A 75-year-old man presented with bilateral upper limb and lower limb numbness for one month. He also had intermittent muscle cramps over both calves for one week. He did not exhibit any body or limb weakness, imbalance, or unsteadiness. There was no history of fever, preceding respiratory or gastrointestinal illness, chest pain, palpitations, or seizures. Additionally, he did not experience arthralgia, rash, weight changes, cold intolerance or lethargy- features that might suggest connective tissue disease or hypothyroidism. His medical history includes ischemic heart disease, for which he underwent coronary artery bypass graft surgery (CABG) in 2014, along with well-controlled diabetes mellitus (HbA1c of 6.7%), hypertension, and dyslipidaemia. His medication includes T. Metformin 250mg BD, T. Bisoprolol 5mg OD, T. Perindopril 8mg OD, T. Amlodipine 10mg OD, T. Cardiprin 100mg OD, T. Isosorbide dinitrate 10mg TDS, T. Trimetazidine MR 35mg BD, T. Atorvastatin 40mg ON and sublingual glyceryl trinitrate as needed. Additionally, he had been on T. Omeprazole 40mg daily for the past ten years for gastroprotection, owing to his concurrent use of cardiprin. He was not on any diuretics. He had no history of alcoholism. He did not have family history of neuromuscular and connective tissue disorders.

On physical examination, he was alert and pink. Vital signs were stable, and no abnormalities were noted on cardiovascular and respiratory examination. Neurological examination revealed reduced pin-prick sensation over the bilateral hands and feet. Power and reflex were normal. Monofilament test was normal. Vibration and proprioception were preserved. Chvostek's sign was negative. A provisional diagnosis of bilateral symmetrical peripheral neuropathy, likely secondary to diabetic neuropathy, was made. Other differential diagnosis includes hypothyroidism, electrolyte or vitamin B12 deficiency. Laboratory investigations included serum magnesium, calcium, phosphate, vitamin B12, and thyroid function tests. However, serum sodium and potassium levels were not assessed initially. The results revealed hypomagnesemia (0.38mmol/L; reference range: 0.66-1.07mmol/L) and hypocalcemia (corrected calcium: 2.04mmol/L; reference range: 2.20-2.60mmol/L). Other blood investigations were normal. Calcium carbonate 1500mg tablets daily was prescribed and the patient was advised on a high magnesium diet. Serum magnesium and calcium, together with serum potassium, were repeated after two weeks. However, serum magnesium and calcium levels showed no improvement, and hypokalaemia was also present. (Table I). Further detailed history was taken to elucidate the cause. Medication reconciliation was notable for omeprazole. Given the patient's history of prolonged PPI use and the exclusion of other potential causes, such as diuretic use, gastrointestinal losses, a diagnosis of PPI-induced hypomagnesemia was made. Since the patient refused admission for intravenous magnesium infusion, he was counselled to discontinue omeprazole and to purchase oral magnesium supplements.

Magnesium levels normalised following a one-month discontinuation of omeprazole, without magnesium

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Table I: Blood investigation results

	08/12/23	15/01/24	15/02/24	08/04/24	10/07/24	17/07/24	26/08/24	12/09/24	21/10/24	Normal range
Magnesium	0.38	0.39	0.75	0.69	0.46	0.70	0.51	0.61	0.76	0.66-1.07 mmol/l
Corrected Calcium	2.04	1.92	2.40	2.33	2.24	2.34	2.25	2.30	2.18	2.20-2.60 mmol/l
Potassium	-	3.2	4.3	4.4	3.4	3.6	4.0	3.9	4.2	3.5-5.1 mmol/l

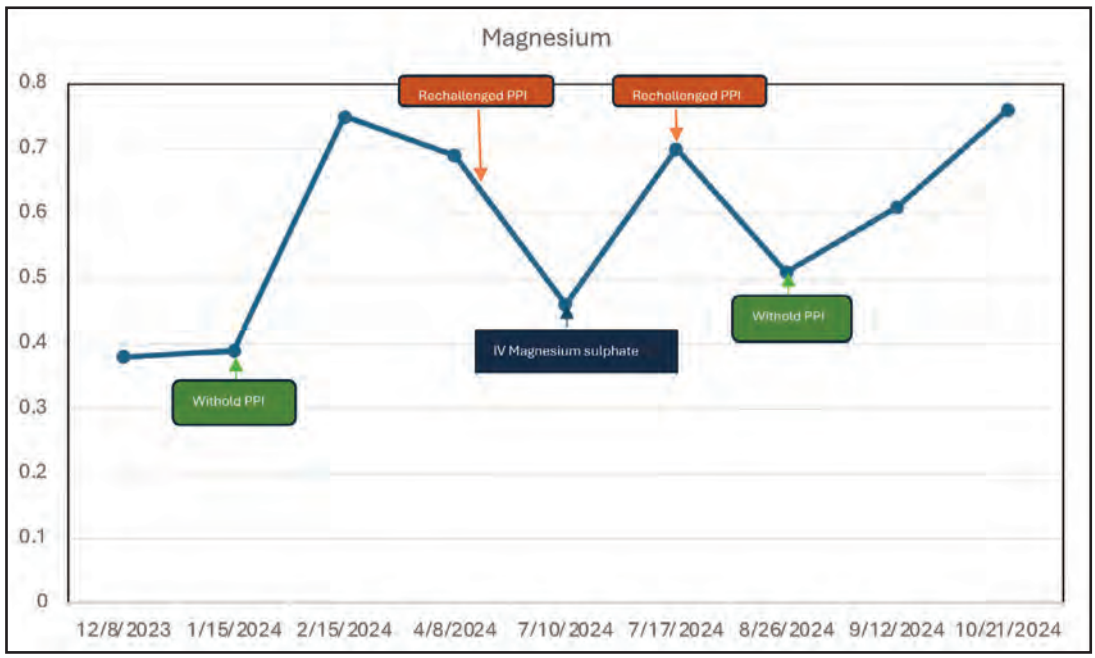

Fig. 1: Patient's serum magnesium levels

supplementation (as the patient did not purchase it), with normal serum magnesium recorded at 0.75mmol/L on 15/02/2024 and 0.69 mmol/L on 08/04/2024. (Table I and Figure 1). However, one month later, he was re-challenged with another type of proton pump inhibitor, T. pantoprazole 40mg OD, as he presented with gastroesophageal reflux disease symptoms. His magnesium level was only monitored after approximately two months of daily pantoprazole use, revealing a decline to 0.46 mmol/L. Around the same time, he experienced recurrent limb numbness. Electrocardiogram (ECG) findings revealed sinus bradycardia, Q wave in lead III and a VF, and T-wave inversions in V2-V4. He was referred immediately for hospital admission. In light of the elevated Troponin I levels, the cardiology team managed the case as non-ST elevation myocardial infarction (NSTEMI). He was corrected with intravenous magnesium sulphate during admission. The patient was started on dual anti-platelet therapy (DAPT), and pantoprazole was prescribed concurrently to reduce the gastrointestinal bleeding risk upon discharge from the hospital. His magnesium level was closely monitored during clinic visits. Serial monitoring revealed a decline in his magnesium levels from 0.87 to 0.51mmol/L within one month of resuming PPI therapy, prompting discontinuation of the medication. Following cessation of PPI, his magnesium levels rose progressively to 0.61 mmol/L after two weeks and reached 0.76 mmol/L over the following month, without magnesium supplementation. (Table I and Figure 1).

The normalisation of magnesium levels following proton pump inhibitor discontinuation, coupled with the recurrence of hypomagnesemia upon PPI resumption, underscores a strong causal relationship between PPI use and hypomagnesemia, regardless type of PPI.

DISCUSSION

Magnesium plays a crucial role in numerous functions in the body, such as bone development, neuromuscular function, signalling pathways, energy storage and transfer, stability of DNA and RNA, and cell proliferation.[3] Despite its importance, magnesium levels are not routinely monitored in patients, leading to its designation as the "forgotten electrolyte".[4] The body's magnesium levels are regulated through three main mechanisms: intestinal absorption, renal reabsorption and excretion, and exchange with the body's magnesium stores, primarily in the bones.[3]

Hypomagnesemia is particularly significant in clinical settings due to its potential to cause neuromuscular disturbances such as tetany, tremors, seizures, involuntary movements and as well as cardiac complications, including atrial and ventricular arrhythmias.[4,5] Other electrocardiogram changes include prolonged PR interval, widening of QRS complex and peaked or flattened T waves.[5] In such instances, it is crucial to perform an ECG to identify any potential cardiac complications, although this was not done in the present case during initial presentation.

Additionally, hypomagnesemia is often accompanied by hypocalcaemia and hypokalaemia, making it challenging to attribute specific clinical symptoms solely to low magnesium levels. It is postulated that magnesium deficiency impairs Na-K-ATPase and enhances renal potassium excretion, leading to hypokalaemia.[4] Various mechanisms have been proposed to explain hypocalcaemia in magnesium deficiency. One theory suggests it is due to reduced secretion of parathyroid hormone (PTH) or resistance to PTH.[5] Potassium or calcium depletion in these cases cannot be corrected until magnesium levels are restored.[4] The metabolic effects of magnesium may render hypocalcaemia and hypokalaemia refractory to treatment if there is concurrent hypomagnesemia.

Proton pump inhibitors are commonly prescribed for the treatment of gastroesophageal reflux disease, peptic ulcer disease, and for the prevention of gastric ulcers in patients requiring prolonged use of nonsteroidal anti-inflammatory drugs or corticosteroids. However, with the growing number of PPI use, the occurrence of adverse effects, including hypomagnesemia, increased risk of kidney, liver, and cardiovascular disease, dementia, susceptibility to respiratory and gastrointestinal infections, and impaired absorption of nutrients has been described consistently.[1] The association of hypomagnesemia and proton pump inhibitors was first described in 2006. Subsequently, several clinical studies were done to identify the association between PPI and hypomagnesemia. A meta-analysis by Srinutta et al., found that individuals who use PPIs are 1.83 times more likely to develop hypomagnesemia compared to those who do not use PPIs.[6] Nevertheless, the exact mechanism of PPI-induced hypomagnesemia remains unclear. The mechanism of proton pump inhibitor-induced hypomagnesemia is believed to be related to impaired intestinal absorption of magnesium, via alteration of intestinal mucosal pH and interference with transient receptor potential melastatin-6 (TRPM6)-mediated active absorption of magnesium.[7] Hypomagnesemia associated with PPI usage generally occurs after prolonged periods of use, usually more than six months.[8] There is also a dose-response correlation between proton pump inhibitor usage and hypomagnesemia. The odds of developing hypomagnesemia are more than twice as high for high-dose PPI users compared to low-dose users.[6] It is also independent of the type of PPI, as in this case, in which patient developed hypomagnesemia with either omeprazole or pantoprazole. In addition, concomitant diuretic usage increases the risk for PPI induced hypomagnesemia.[8]

Proton pump inhibitor is often co-prescribed in patients on dual antiplatelet therapy to reduce gastrointestinal bleeding risk. The concurrent use of DAPT and PPIs remains a topics of debate, with international guidelines offering varying recommendations on their concurrent use.[9] Therefore, PPI therapy should be individualised based on a patient's risk profile, with careful consideration of indication and treatment duration, for patients intolerant or contraindicated to PPIs, alternative gastroprotective agents such as H2-receptor antagonists or misoprostol may be considered, though these alternatives are less effective than PPIs for long-term management.[10]

The treatment of hypomagnesemia in patients depends on the degree of hypomagnesemia and the severity of symptoms. Oral magnesium is the preferred route of administration for patients with no or minimal symptoms. However, many patients are intolerant to oral magnesium due to side effects such as gastrointestinal discomfort and diarrhoea. Examples of oral magnesium include magnesium gluconate, magnesium oxide, magnesium carbonate, and magnesium gluconate. Intravenous magnesium repletion is the preferred route of administration in symptomatic hypomagnesemia. At the same time, the underlying cause should be corrected. Although magnesium levels transiently returned to normal after supplementation, recurrences were frequent in patients who continued on PPI. PPI withdrawal remains the gold standard to restore hypomagnesemia in PPI users.[7]

CONCLUSION

Clinicians should be aware of the potential for hypomagnesemia in patients on PPI, especially those on long-term PPI. Regular monitoring of serum magnesium levels may be warranted in these patients, especially if they exhibit symptoms suggestive of electrolyte imbalance. Additionally, regularly reviewing the indication for continued PPI use is also important to reduce the overuse of PPI. Educating and empowering prescribers and patients about the rationale for deprescribing is essential to ensure the success of this approach.

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CONFLICT OF INTEREST

None

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