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CHRONIC PROTON PUMP INHIBITOR USE LEADING TO REFRACTORY HYPOMAGNESAEMIA IN A PATIENT WITH RHEUMATOID ARTHRITIS: A CASE REPORT

Rizwanullah[1]*, Muzamil Khan[2], Radhika Bassi[3], Samah Badr Hamad[4], Reem Eisa[5], Henna Patel[6]

[1]Department of Medicine, Hayatabad Medical Complex, Pakistan
[2]Department of Medicine, GW School of Medicine and Health Sciences, USA
[3]Department of Medicine, Ross University School of Medicine, Barbados
[4]Department of Basic Medical Sciences, University of Khartoum, Sudan
[5]Department of Medicine, Ain Shams University, Egypt
[6]Department of Medicine, GMERS Hospital, India

***Corresponding Author:** Rizwanullah
*Email address: urizwan600@gmail.com

Abstract:
The widespread utilization of proton pump inhibitors has surged in recent times, making them one of the most frequently prescribed medications. Magnesium, a crucial intracellular cation, contributes to numerous cellular functions. Depleted magnesium levels can trigger a range of adverse events. The cause of hypomagnesaemia associated with proton pump inhibitors remains uncertain. A 43-year-old female presented Out Patient Department (OPD) of Hayatabad Medical Complex, with a range of symptoms including weakness, anorexia, lethargy, tremor, and muscle fasciculation. She is a diagnosed case of Rheumatoid Arthritis. Following her Rheumatoid Arthritis diagnosis, she commenced prednisone treatment, which induced epigastric pain. Consequently, she initiated proton pump inhibitors usage for a prolonged period of 12 years, leading to PPI-induced hypomagnesaemia. The objective of this study is to avoid unnecessary use of PPIs and if someone use it for chronic condition then Magnesium level should be assessed during that time to avoid any dreadful complication of hypomagnesaemia like arrhythmias.

Keywords: Proton pump inhibitors, PPI-induced hypomagnesaemia, magnesium depletion, rheumatoid arthritis, prolonged PPI usage, Hayatabad Medical Complex, refractory hypomagnesaemia, intravenous magnesium supplementation.

Introduction:

Proton pump inhibitors (PPIs) are a type of medication characterized by their lipophilic nature and weak basic properties. They possess the ability to traverse the membrane of parietal cells within the stomach. Once inside the acidic environment of the parietal cell canaliculus, PPIs undergo protonation, transforming into their activated sulphenamide form. This activated form then binds covalently to the hydrogen-potassium adenosine triphosphatase enzyme system present in gastric parietal cells. This binding action results in the irreversible inhibition of acid secretion [1-3]. The widespread utilization of proton pump inhibitors (PPIs) has surged in recent times, making them

one of the most frequently prescribed medications. For instance, PPIs currently represent close to 10% of the annual prescription expenses totaling £4.5 billion in England [4].

Magnesium, a crucial intracellular cation, contributes to numerous cellular functions. Depleted magnesium levels can trigger a range of adverse events, encompassing symptoms such as vomiting, diarrhea, cramps, convulsions, bradycardia, and in severe cases, fatality. The cause of hypomagnesaemia associated with proton pump inhibitors (PPIs) remains uncertain, though one suggested explanation is the potential impact of prolonged PPI usage on the absorption of magnesium in the intestines [5,6].

Here we present a case who exhibited refractory PPI-induced hypomagnesaemia, despite receiving sustained oral and intravenous magnesium supplementation.

Case Report:

The 43-year-old female presented at Hayatabad Medical Complex, Peshawar with a range of symptoms including weakness, anorexia, lethargy, tremor, and muscle fasciculation. She has been managing diabetes for 8 years, hypertension for 5 years, and Rheumatoid Arthritis for a decade.

Following her Rheumatoid Arthritis diagnosis at age of 31 years, she was using oral prednisone at a dose of 10mg/day and oral diclofenac 50mg twice day, oral omeprazole 40mg once daily for a decade. She had no history of diuretic intake. On examination she had fasciculation, hyperreflexia grade +3. Rest all examination were unremarkable. All her labs investigations were normal including serum sodium, potassium and chloride. Her labs investigation showed persistent hypomagnesemia but urinary magnesium were low, excluding renal cause of hypmagnesemia. Previously, she underwent multiple hospitalizations due to this issue, where she received Mg oral tablets and IV ampoules. Serum Mg level during patient's stay in different hospitals is given in table 1.

Table 1:

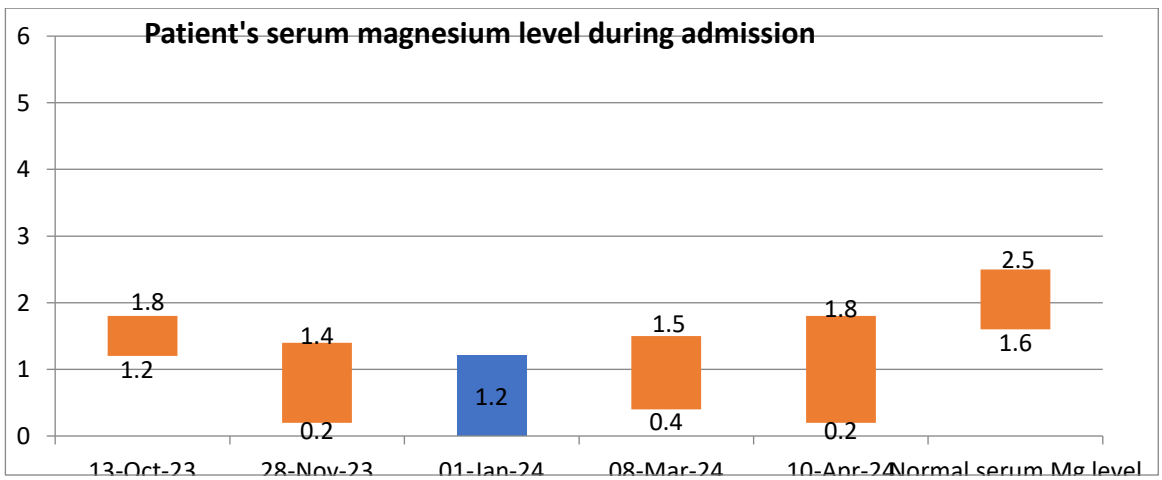
Date of admission	Mg levels during admission(mg/dl) ***	Total dose of Mg replenishment	Mg level after Mg replenishment
13 Oct 2023	1.2-1.4	10 ampoules* + 6** tablets	1.3-1.5
28 Nov 2023	0.2-1.2	7 ampoules	0.4-1.4
1 Jan 2024	0.8-1.3	15 ampoules	0.9-1.3
8 March 2024	0.4-1.5	10 ampoules	0.6-1.6
10 April 2024 (current admission)	0.2-1.1	25 ampoules + 8 tablets	0.4-1.3

Table 1: Magnesium level during different hospitalizations

*1 ampoule (2ml) of Mg contains 1000mg of magnesium, about 2 millimoles magnesium ions (Mg^{2+}) per ml.

**1 oral Mg tablet contain about 520 mg of magnesium lactate dehydrate

***Normal serum Mg level is 1.6-2.5 mg/dl



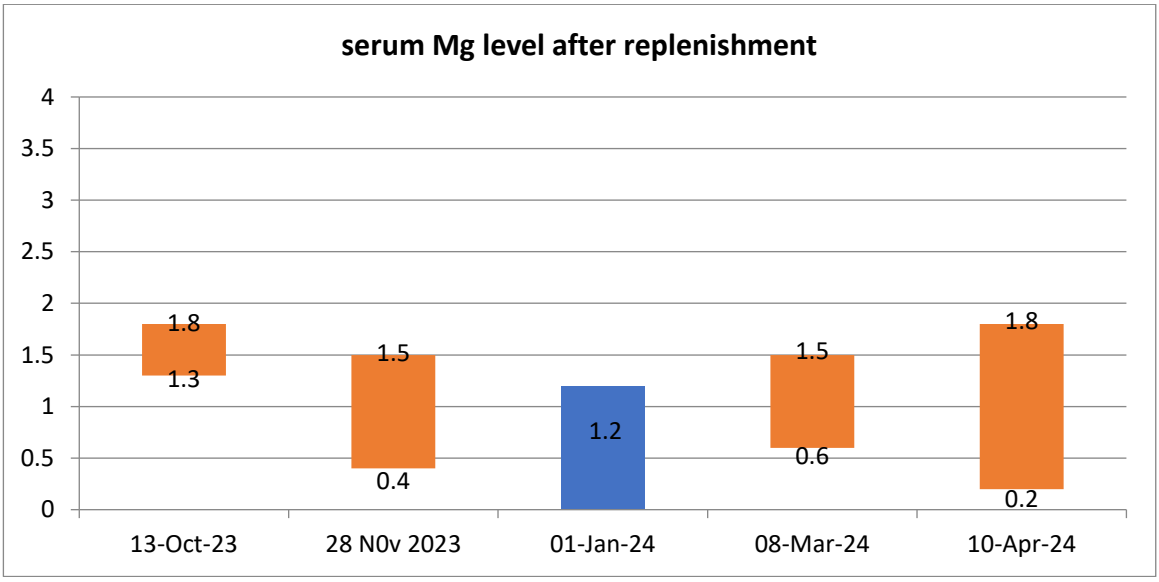


Figure 1: Magnesium level before and after replacement during multiple hospitalizations

From literature studies, it has been concluded that Proton Pump Inhibitors (PPIs) are associated with hypomagnesemia. Our case presented during different hospitalizations with hypomagnesemia but was refractory to replenishment. Close monitoring of magnesium levels is suggested in these patients as hypomagnesemia can present with life-threatening arrhythmias.

Discussion:

PPIs are classified as weak bases, a chemical property that facilitates their migration from the bloodstream to the highly acidic environment of the secretory canaliculi, where the pH approximates one. Research indicates that the concentration of PPIs at the luminal surface of the H+/K+ ATPase pump surpasses their blood concentration by a factor of 1,000, significantly contributing to their therapeutic efficacy [7].

Therefore, PPIs are widely regarded as safe and highly efficacious medications. They selectively accumulate at their intended site of action, activate only in low pH environments, outperform histamine H2-receptor antagonists in suppressing gastric acid secretion, and exhibit inhibitory activity far exceeding their plasma half-life [8].

The mechanism of PPI-induced hypomagnesemia is believed to originate from disrupted activity of the transient receptor potential melastatin 6/7 (TRPM6/7) channels. These channels play a crucial role in absorbing magnesium in the intestines, particularly in response to lower pH levels. Prolonged use of PPIs can disrupt normal intestinal pH levels, thereby affecting TRPM6 channel function. This disruption results in a decreased affinity of TRPM6 proteins for magnesium ions, directly leading to hypomagnesemia. Additionally, genetic predispositions, such as certain common single nucleotide polymorphisms in the TRPM6 gene, can exacerbate this condition. Individuals with these genetic variants face a 5.8-fold increased risk of developing hypomagnesemia when using PPIs chronically [9].

Furthermore, the decrease in magnesium (Mg^{2+}) solubility resulting from higher pH levels, and the subsequent reduction in Mg^{2+} absorption, are thought to be significant factors in the pathophysiology of PPI-induced hypomagnesemia (PPIH). This elevated pH environment leads to increased affinity of Mg^{2+} ions for binding to negatively charged ions like Cl^- and PO_4^{3-}, resulting in a significant decrease in Mg^{2+} solubility and availability for absorption in the intestines [10].

The association between proton pump inhibitor (PPI) usage and hypomagnesaemia was initially identified within the scientific realm via a case report published in 2006[10]. Since then, many case studies have confirmed this connection, regardless of additional electrolyte imbalances. These reports commonly depict individuals who have been chronically exposed to PPIs, exhibiting

symptoms indicative of hypomagnesaemia, such as arrhythmias, as well as signs of neuroexcitability like seizures and tetany [11].

Estimates indicate that prescriptions for PPIs exceed 100 million annually. The growing number of reports linking proton-pump inhibitors to hypomagnesaemia, alongside early case studies, prompted the United States Food and Drug Administration to issue a "drug safety communication" in 2013[11].

We strongly attribute the prolonged use of PPIs, along with the high dosage administered (40 mg/day, and occasionally 40 mg twice daily), as the primary factor contributing to this instance of PPIH. Throughout the multiple hospitalizations, serum magnesium levels were consistently monitored and emphasized ongoing follow-up, along with discontinuation of PPI use upon each discharge from the hospital.

Conclusion:

To conclude, this case highlights the complex relationship between medication usage, chronic medical conditions, and electrolyte imbalances. Despite receiving oral and intravenous magnesium supplementation, the patient's persistent hypomagnesaemia suggests a significant underlying condition. Healthcare providers must remain vigilant for adverse effects of long-term medication use, particularly regarding electrolyte balance. Further research into the mechanisms and management of PPI-induced hypomagnesaemia is warranted to optimize patient care.

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