

# Proton Pump Inhibitors: Uncovering the Mystery Behind Refractory Severe Hypocalcemia - A Case Report

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## ABSTRACT

Proton pump inhibitors (PPIs) are commonly prescribed drugs to reduce gastric acid secretion and treat a variety of gastrointestinal disorders. Hypomagnesemia has been reported with long-term PPI use. We report a case of long-term PPI use associated with refractory severe hypocalcemia secondary to a normo-magneseemic tissue magnesium deficiency. The patient presented with clinical symptoms of spasms and perioral tingling along with prolongation of QTc interval on electrocardiogram. On failure of intravenous (IV) calcium therapy, the patient improved after a trial of IV magnesium therapy. It is crucial in clinical practice to be aware of adverse events of long-term PPI therapy.

**Keywords:** Carpopedal spasm, Chvostek sign, Magnesium Sulfate, Pantoprazole, Proton Pump Inhibitor, Tetany, Trousseau sign

\*See End Note for complete author details

## INTRODUCTION

Proton Pump Inhibitors (PPI) are commonly prescribed drugs that act by inhibiting H(+)-K(+)-Exchanging ATPase. These drugs, which are prescribed for gastroesophageal reflux disease, peptic ulcer disease, etc., are associated with various adverse effects. Hypomagnesemia has been reported with long-term PPI use.<sup>1</sup> However, the incidence rate and mechanism are still unclear.<sup>2</sup> Hypomagnesemia, may cause neuromuscular and cardiac complications, hypoparathyroidism, bone metabolic diseases, and concurrent electrolyte disorders (mainly hypocalcemia and hypokalemia).<sup>3</sup> Here, we report a case of long-term PPI use associated with refractory severe hypocalcemia that improved after a trial of intravenous (IV) magnesium in a patient with a normo-magneseemic tissue magnesium deficiency.

## CASE REPORT

A 65 year old female, presented to the emergency department with perioral tingling sensations for 5 days and spasms in her hands for 2 days. She has had a history of gastroesophageal

reflux disease (GERD) and dyspepsia for 10 years, for which she has been taking Tab. Pantoprazole 40 mg PO OD. She was not suffering from any other comorbid conditions. Also no history of diuretic or recent antimicrobial agent use and no history suggestive of malabsorption syndromes. She also denied any history of alcohol, tobacco and recreational drug abuse. On examination, the Chvostek sign and Trousseau sign (**Figure 1**) were positive. No other significant findings were observed on examination. Laboratory investigations are mentioned in **table 1**.

The electrocardiogram (ECG) had QT prolongation (**Figure 2**). Arterial blood gas analysis and kidney and liver function tests were normal. The laboratory investigations are as shown in **Table 1**. Renal ultrasound was normal. Various tests to rule out etiology of hypocalcemia were normal or borderline normal as seen in **Table 1**.

The patient was treated with IV calcium gluconate (90 mg elemental calcium given over 20 minutes, followed by a repeat dose after 60 minutes, followed by 2400 mg elemental calcium over 48 hours at a rate of 50 mg/hr). Over the next two days, there was no significant improvement in both clinical symptoms and the serum calcium level.

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**Figure 1. Showing a positive Trousseau's sign for latent tetany in the setting of hypocalcemia. The sign is observable as a carpopedal spasm induced by ischemia secondary to the inflation of a sphygmomanometer cuff to 20 mmHg over the systolic blood pressure for 3 minutes**

Considering the possibility of tissue magnesium deficiency, she underwent a trial of IV magnesium sulphate (2 g/day for 2 days). After 24 hours, the ECG changes reverted (Figure 3), and she became asymptomatic. This therapeutic trial affirmed us to possibly ascertain the cause of hypocalcemia to be tissue magnesium deficiency. She was continued on oral calcium and magnesium supplements and was observed for the next two days. She remained asymptomatic and was later discharged. She was advised to stop PPI, make lifestyle modifications with respect to GERD, and take antihistamine drugs (Ranitidine) as needed. On a follow-up visit after 3 months, she had normal serum calcium levels.

**Table 1. Laboratory Investigations (\*abnormal)**

Laboratory Parameter	Result	Laboratory Reference Range
25-OH Vit D	22 ng/ml	22- 40 ng/ ml
Albumin	3.5 g/dl	3.5 to 5.0 g/dl
Calcium	6.6 mg/dl*	8.5–10.5 mg/dL
Chloride	101 mEq/L	96 to 106 mEq/L
Free T3	2.600 pg/ml	2.3-6.6 pg/ml
Free T4	1.100 ng/dl	0.8-1.8 ng/dl
Ionised Calcium	0.54 mmol/lit*	1.12-1.32 mmol/lit
Magnesium	1.8 mg/ml	1.6-2.8 mg/dl
Phosphorus	3.3 mg/dl	2.5–4.5 mg/dL
Potassium	3.6 mEq/L	3.5-5.2 mEq/L
Serum PTH	10.3 pg/dl*	11-69 pgm/dl
Sodium	137 mEq/L	135-145 mEq/L
Total Proteins	6.3 g/dl	6 to 8 g/dl
TSH	7.170 uIU/ml	0.4-4 uIU/ml
Urinary Calcium	2.16 mg/dl*	4.5 – 5.3 mg /dl
Male Literacy Rate (%) *	88.33	82.14
Female Literacy Rate (%) *	70.70	65.46

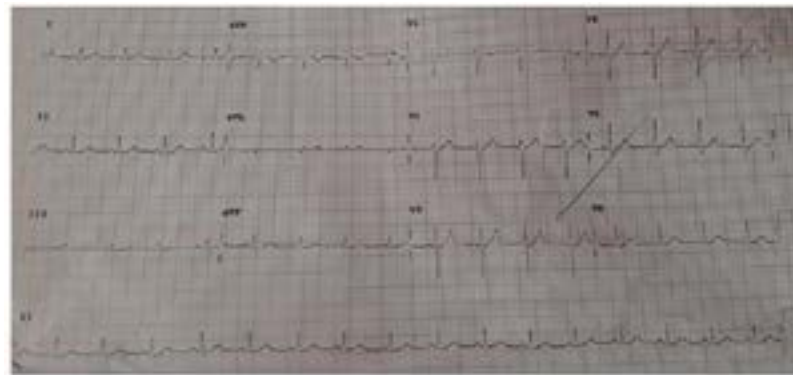
## DISCUSSION

Proton pump inhibitors (PPIs), with or without prokinetic agents, are now among the most rampantly prescribed drugs.<sup>4</sup> They are used to reduce gastric acid secretion and treat a variety of gastrointestinal disorders, such as GERD, peptic ulcer disease, and *Helicobacter pylori* infection. However, a recent meta-analysis has shown that PPI use is associated with an increased risk of hypomagnesemia, a potentially serious electrolyte imbalance.<sup>5</sup> In current clinical practice, many patients with symptomatic GERD are treated empirically with medications without prior endoscopy, i.e., without knowledge of whether the patient has erosive or nonerosive reflux disease.<sup>6</sup>

Severe hypocalcemia, which is defined as serum calcium <7.6 mg/dL, is an emergency with the risk of life-threatening cardiac arrhythmias or seizures. Refractory hypocalcemia is resistant to standard intravenous calcium therapy. The possibility of normo-magnesemic magnesium depletion (in which there is isolated cellular magnesium depletion) should be considered as a possible cause of refractory hypokalemia or unexplained hypocalcemia in patients at high risk for magnesium loss.<sup>7</sup> The concentration of serum magnesium is closely regulated. Because only 1% of body magnesium resides in the extracellular fluid, measurements of serum magnesium levels may not accurately reflect the level of total body magnesium stores. Hypomagnesemia is defined as a serum magnesium level below the normal range



**Figure 2. Electrocardiogram (ECG) at the time of presentation showing prolonged QTc interval (480 msec)**



**Figure 2. Electrocardiogram (ECG) 24 hours after IV Magnesium therapy showing normal QTc interval (<460 msec)**

of 1.7 to 2.2 mg/dL. The symptoms of hypomagnesemia can range from mild muscle weakness and cramping to seizures, cardiac arrhythmias, and even death. Several case reports and observational studies have linked PPI use to hypomagnesemia, with some studies reporting an incidence as high as 50% in patients on long-term PPI therapy.<sup>8</sup>

The mechanism by which PPIs cause hypomagnesemia is not fully understood, but several hypotheses have been proposed.<sup>9</sup> One theory suggests that PPIs may interfere with the absorption of magnesium in the gastrointestinal tract by reducing the acidity of the stomach, which is necessary for the solubilization and ionization of magnesium salts. Another theory suggests that PPIs may affect the expression of certain transport proteins involved in magnesium homeostasis, leading to decreased magnesium reabsorption in the kidneys.<sup>10</sup>

Despite the growing body of evidence linking PPI use to hypomagnesemia, the true incidence of this adverse effect is still unclear, and more research is needed to fully understand the underlying mechanisms. However, it is important for

clinicians to be aware of this potential risk and to monitor patients on long-term PPI therapy for signs and symptoms of hypomagnesemia.

## CONCLUSION

In conclusion, PPIs are a widely prescribed class of drugs that have been shown to be effective in treating a variety of gastrointestinal disorders. However, their use has been associated with an increased risk of hypomagnesemia, which can have serious consequences if left untreated. Clinicians should be aware of this potential adverse effect and monitor patients on long-term PPI therapy for signs and symptoms of hypomagnesemia. The possibility of normo-magnesium magnesium depletion should be considered as a possible cause of refractory hypokalemia or unexplained hypocalcemia in patients at high risk for magnesium loss.

## END NOTE

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