

CASE REPORT

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Hypomagnesemia and hypocalcemia due to long standing proton pump inhibitor use: A severe side effect of a commonly prescribed drug

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ABSTRACT

Proton pump inhibitors (PPIs) are amongst the most prescribed medications in Canada. However, they are not without risk. While there are many acute and chronic reasons for the use of these drugs, they are often prescribed with no clear indication. In this case, we describe a patient who chronically used a PPI and presented with severe hypomagnesemia and profound hypocalcemia, which caused a collapsed esophagus. After extensive workup, it was deemed that his electrolyte imbalances were most likely due to his chronic PPI use, and his symptoms quickly improved with electrolyte replacement and cessation of the drug. This case illustrates the importance of judicious use of even the most used medications and argues for monitoring of electrolytes for those who use PPIs chronically.

LEARNING POINTS

- Review the many side effects associated with a commonly prescribed medication class: proton pump inhibitors, and review indications for their use.
- Reinforce the importance of deprescribing unnecessary medications.
- Emphasize the importance of keeping adverse drug reactions in the differential when assessing electrolyte abnormalities.

KEYWORDS

Adverse drug reaction, Deprescribing habits, Electrolyte Imbalances

1 | INTRODUCTION

Proton pump inhibitors (PPIs) are commonly used medications, being the second most prescribed drug class in Canada behind statins, with 2.7 million users being prescribed these medications in 2021 alone (1). PPIs have several acute and chronic indications. Acute in-

dications include duodenal and gastric ulcer treatment, part of the triple therapy regimen for *Helicobacter pylori* infections, and stress ulcer prophylaxis in critically ill patients. Indications for long-term usage include previous GI bleed, severe (Grade D) esophagitis, prevention of nonsteroidal anti-inflammatory drug-induced ulcers, and hypersecretory conditions such as Zollinger-Ellison

syndrome (2, 3, 4). Evidence shows that PPIs are, for the most part, safe in the short-term, with the serious adverse events tending to be associated with chronic use. In a large claims-based analysis of over 1.7 million adults, approximately 28% of newly prescribed proton pump inhibitor (PPI) courses were classified as potentially inappropriate based on cumulative dose and duration exceeding guideline recommendations (5). The incidence of potentially inappropriate PPI prescribing increased over time, rising from 4.8% to 6.4% of the general population between 2013 and 2017 (5). This all together results in a significant population using PPIs chronically. Documented adverse effects of long-term PPI therapy include increased susceptibility to enteric infections (such as *Clostridioides difficile*), community-acquired pneumonia, micronutrient deficiencies such as hypomagnesemia and vitamin B12 deficiency, and impaired calcium absorption with an associated risk of osteoporotic fractures. These drugs have also been linked to acute interstitial nephritis that could lead to the development of chronic kidney disease. Additional reported associations include small intestinal bacterial overgrowth and possible cardiovascular, cognitive, and renal effects, though the strength of evidence varies across these conditions (4, 6). Furthermore, PPIs further complicate polypharmacy by having a myriad of drug interactions and affecting the absorption of other medications due to their effects on the gastric pH (7). These adverse events can easily be missed among chronic users in the community, and this can have dangerous consequences, as illustrated in the case below.

2 | CASE DESCRIPTION

The patient was a 75-year-old male known for chronic obstructive pulmonary disease (COPD), hypertension, a history of previous cerebrovascular accident, C7 radiculopathy, and severe GERD. He presented to the hospital with shortness of breath and stridor in the context of severe worsening dysphagia to liquids in the past three weeks. The patient decided to come to the emergency department as he felt his "throat was closing up". He in-

dicated that he also had experienced involuntary hand spasms the day before presentation and had paresthesia in his hands and feet in the past couple of weeks. He denied any nausea, vomiting, diarrhea, constipation, weight loss, fevers, or night sweats. He was previously well until his symptoms started.

His medications at home included Aspirin 80 mg daily, Bisoprolol 5 mg daily, Atorvastatin 40 mg daily, Amlodipine 5 mg daily, Valsartan 160 mg daily, Magnesium Gluconate 500 mg daily, and Calcium Carbonate 500 mg daily, as well as Pantoprazole 40 mg daily. He endorsed taking Pantoprazole daily for the past five years. His hypomagnesemia had been noted as a previous concern, and as such, he was already prescribed magnesium supplementation by his primary care provider.

Physical examination revealed a man with slightly increased work of breathing but otherwise well. His blood pressure was 138/78 mmHg, his heart rate was 65 bpm and his oxygen saturation was 95% on room air. There was no tetany found on neurological examination and he had a negative Chvostek's sign but had a positive Trousseau's sign. His electrocardiogram at presentation showed a prolonged corrected QT interval of 474 ms.

Initial laboratory tests showed that he had severe hypomagnesemia at 0.21 mmol/L (normal: 0.70-1.23 mmol/L) and severe corrected hypocalcemia at 1.21 mmol/L (normal: 2.12-2.62 mmol/L). A CT scan of his head and neck demonstrated a collapsed esophagus but no other major abnormalities. Given his severe electrolyte disturbances, he was given 5 g of intravenous (IV) magnesium as well as 1 g of IV calcium gluconate.

At this point, the etiology of his electrolyte abnormalities was unclear and the differential for these abnormalities was quite broad. Hypomagnesemia is normally caused by one of three reasons: decreased intake, increased excretion, or sequestration. Decreased intake is often in the context of malnourishment, cachexia, or severe alcoholism. Sequestration is caused by shifts of magnesium from extracellular to intracellular compartments, often in the context of an acute correction from a metabolic insult, such as diabetic ketoacidosis treatment, correction of acidosis, or refeeding syndrome. Fi-

Laboratory Investigations	Result	Reference Range
Serum parathyroid hormone	127 ng/L	10-70 ng/L
Serum vitamin D-O25	86 nmol/L	75-250 nmol/L
Serum 1-25 Vitamin D	60 pmol/L	90-174 pmol/L
Urine magnesium	2.8 mmol/day	3.0-5.0 mmol/day
Urine potassium	22 mmol/day	25-125 mmol/day
Urine calcium	3.01 mmol/day*	2.5-7.5 mmol/day
Urine creatinine	8.8 mmol/day	7.1-15.9 mmol/day

* Urinary calcium was not as low as expected due to urine tests being done after calcium replacement.

TABLE 1 Results of investigations to assess the cause of hypocalcemia and hypomagnesemia

nally, increased excretion is either through the GI tract (laxative abuse, diarrheal illnesses, malabsorption syndromes) or the kidney (diuretic use, renal injury/failure, or congenital disorders such as Gittleman's) (8).

On the other hand, hypocalcemia can be caused by several reasons. When approaching hypocalcemia, one can divide causes into PTH dependent, PTH independent, and other causes. PTH dependent causes involve hypoparathyroidism and the disruption of the body's ability to regulate calcium homeostasis. This is often due to the destruction or removal of the parathyroid gland. PTH independent causes of hypocalcemia are varied and include certain drugs (Foscarnet and bisphosphonates), Vitamin D deficiency, metabolic abnormalities (severe acidosis and alkalosis) and severe illness states such as sepsis and pancreatitis. Moreover, hypomagnesemia itself can be a cause of hypocalcemia, as low magnesium can cause induced PTH resistance (9).

Further investigation was done to elucidate the etiology of hypomagnesemia and hypocalcemia (Table 1). The serum investigations yielded appropriately high PTH, sufficient levels of vitamin D-25 OH and low levels of 1-25 Vitamin D. This indicated secondary hypoparathyroidism, likely secondary to hypomagnesemia. The urine electrolytes showed low levels of magnesium, low levels of potassium, and normal levels of calcium. This was indicative of no renal wasting of electrolytes, which made a renal pathology less likely. Thus, upon

consultation with Nephrology and Endocrinology, it was determined that the etiology was likely chronic proton pump inhibitor use, causing poor absorption and increased excretion of magnesium through the patient's GI tract.

The patient was admitted to an Internal Medicine ward and given IV replacement of magnesium and calcium. The proton pump inhibitor (pantoprazole) was discontinued, and the patient was prescribed H2 antagonists for his gastric reflux symptoms. Within two days, the patient's magnesium and calcium levels normalized. His symptoms resolved, and he was discharged home with close follow up with Endocrinology as well as an outpatient Gastroenterology consultation for investigation of his refractory gastroesophageal reflux.

The patient was seen in the clinic one week after discharge with follow up blood work, and his magnesium and calcium levels were stable and within normal limits. However, he continued to have severe GERD, which will be assessed by his Gastroenterologist.

3 | DISCUSSION

Despite being generally well tolerated medications, PPIs are not without risk. There are both known and unknown side effects of PPI use. Complications from chronic PPI use, such as acute interstitial nephritis, malabsorption of micronutrients and vitamins, and gastric

hyperplasia, are well documented (6, 7). However, there are widespread theoretical risks associated with gastric hypoacidity and disruption of the intestinal microbiota. Observational studies have found an association between PPI use and an increased risk for *Clostridium Difficile* infection, liver disease, and dementia (6). The pathophysiology of these side effects is not well understood. It is thought that the decrease in the acidity of the gastric pH can cause malabsorption of nutrients since many depend on being bound by proteins to be absorbed, and changes in acidity can cause proteins to misfold and decrease absorption (6). Moreover, mechanistically, an increase in gastric pH has been proposed to decrease gastric protection to harmful bacteria and change gut microbiota composition (6). The effects of microbiome-human host interaction is an evolving field, but the modification in this interaction is thought to be the culprit of many of the side effects seen in PPIs (6). Thus, it can be confidently said that we do not yet know the side effects and possible implications of chronic PPI use.

The dangers of inappropriate PPI use are a well-recognized issue, and current recommendations exist to reduce unnecessary use of these medications. For example, PPIs are a part of the American Geriatrics Society Beer's Criteria® for potentially inappropriate medications (10). In addition, efforts are being made to encourage physicians to deprescribe these medications (2, 3). However, the uptake for this has been slow, and these medications are still quite commonly prescribed in an inappropriate manner. Therefore, it is important for physicians to always consider deprescribing and to have frank discussions with their patients about the risks and benefits of these medications. As such, every patient encounter is an opportunity to deprescribe.

Despite the proven side effects of PPIs, current guidelines do not recommend routine laboratory monitoring for patients on chronic proton pump inhibitor therapy. In fact, the expert opinion is that the best way to avoid long term complications of PPIs is to avoid prescribing them inappropriately and prescribing the minimum effective dose when they are indicated (11). As a result, for the clinician who encounters patients in the

inpatient setting with unexplained electrolyte abnormalities, it is important to keep the adverse effects of proton pump inhibitors in their differential.

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