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CASE REPORT

Seizure and Takotsubo Cardiomyopathy Due to Proton Pump Inhibitor

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Abstract

Proton Pump Inhibitor (PPI)-induced hypomagnesemia, first described in 2006, has gained increasing recognition in recent years as a potentially life-threatening adverse event. In comparison to histamine-2 receptor antagonists (H2RA), PPIs exhibit a higher frequency of electrolyte abnormalities, including hypomagnesemia, hypocalcemia, hypokalemia, and hyponatremia; hypomagnesemia is the most common. We report a case of an 80-year-old woman who presented with generalized weakness and diarrhea. She was found to have multiple electrolyte abnormalities that failed to resolve even after the resolution of diarrhea and resumption of feeding. However, her condition improved within one week of discontinuing PPI medication. Her hospital course was complicated by a seizure, attributed to alterations in ionic gradients across cellular membranes affecting neuronal discharge and facilitating epileptiform activities. Additionally, she experienced Takotsubo cardiomyopathy due to decreased myocardial contractility, both in the context of electrolyte imbalance induced by prolonged PPI use.

Keywords: Proton pump inhibitor, Hypomagnesemia, Histamine-2 receptor antagonists, Electrolyte abnormalities, Seizure, Takotsubo cardiomyopathy

1. Introduction

While proton pump inhibitors (PPIs) are intended for acute disorders such as gastric ulcers and esophagitis, they are frequently used for extended periods and are deemed safe for over-the-counter access, in practice.[1] Hypomagnesemia is a potentially serious side effect of PPIs, accounting for approximately 1% of all the adverse events.[2] PPI users have a 40–80% higher risk of developing hypomagnesemia compared to non-users.[2] PPIs reduce the activity of a protein called transient receptor potential melastatin (TRPM) 6, which is situated on the apical membrane of enterocytes.[3] This protein plays a role in facilitating the absorption of magnesium in the intestines, thereby disrupting the process of intestinal magnesium absorption.[2,3]

Magnesium, the most abundant intracellular cation, plays a crucial role in regulating potassium and calcium channels in the heart, muscle, and neurons. The primary clinical manifestations of hypomagnesemia include neuromuscular irritability, CNS hyperexcitability, and cardiac arrhythmias.[4] Hypomagnesemia due to the use of PPIs may be underdiagnosed due to infrequent measurement of magnesium in routine clinical analyses.[5] This underscores the importance of monitoring and controlling unnecessary and prolonged PPI use, as well as regularly assessing serum electrolyte concentrations.

2. Case presentation

An 80-year-old woman presented to the emergency department with progressively worsening dizziness and generalized weakness for one week. There were no associated exacerbating or alleviating factors, and she reported no exposure to new medications or changes in the baseline dosing of pre-existing medications. She denied tinnitus or hearing problems but reported ongoing non-bloody diarrhea, with 4–5 episodes per day for the past week. She is a non-smoker and denied use of recreational drugs or alcohol.

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Medical history was notable for COPD, atrial fibrillation, type 2 diabetes mellitus, and recurrent lower gastrointestinal bleeding due to diverticulosis. Approximately one month prior to presentation, she was admitted due to weakness and was found to be in new onset atrial fibrillation; laboratory diagnostics demonstrated hypokalemia and hypomagnesemia. Her atrial fibrillation was attributed to the noted electrolyte derangements secondary to reduced oral intake and chronic hydrochlorothiazide use. Her electrolytes were repleted, hydrochlorothiazide was discontinued, and she was discharged. Home medications include apixaban, pantoprazole, atorvastatin, metoprolol, and a Symbicort ® inhaler.

On presentation, the patient was afebrile and hypotensive (80/50 mm Hg), with a preserved oxygen saturation in the room air. While initially alert, responsive, and capable of spontaneous conversation per emergency medical service (EMS), upon emergency department evaluation she was subsequently noted to have tonic-clonic movements and eye deviation that persisted for less than 2 min, prompting the administration of intramuscular Lorazepam 2 mg. Her hypotension showed minimal response to two boluses of Ringer's lactate, following which norepinephrine was initiated. In the postictal state, the patient was unable to control her secretions with excessive drooling, and her Glasgow Coma Scale score was 7. Consequently, she was intubated and admitted to ICU.

Cardiopulmonary examination demonstrated atrial fibrillation with rapid ventricular response, with no evidence of peripheral edema, JVP elevation, or adventitious breath sounds. Laboratory diagnostics were remarkable for hypomagnesemia (0.5 mg/dL, reference range: 1.6–2.6 mg/dL), hypokalemia (2.2 mmol/L, reference range: 3.4–4.5 mmol/L), and hypocalcemia (5.5 mg/dL, reference range: 8.7–10.4 mg/dL) (Table 1). Spot EEG showed mild to moderate diffuse slowing in bilateral cerebral hemispheres concerning for a metabolic disturbance without epileptiform discharges. CT head and neck without contrast demonstrated no acute intracranial abnormality and no evidence of large vessel occlusion. Subsequent MRI was also negative. The new-onset seizure was considered to be associated with electrolyte derangement secondary to diarrhea, and maintenance antiepileptic medication was deemed unnecessary.

The patient was gradually weaned off pressors; however, she required higher ventilatory support. Additionally, 1+ pitting edema was observed on bilateral lower extremities, prompting ordering of B-type natriuretic peptide (BNP), which was elevated at 307 pg/mL (normal range: 0–99 pg/mL). Chest radiograph revealed an enlarged cardiac silhouette with increased interstitial markings. The electrocardiogram demonstrated atrial fibrillation with a rapid ventricular response of 138 bpm and a low-voltage QRS complex with a prolonged QTc of 554 ms. The echocardiogram revealed a new onset of moderately reduced left ventricular function (ejection fraction of 40%–45%) with a severely akinetic apical segment and apical ballooning, raising concerns for stress-induced cardiomyopathy (Fig. 1). She received diuretics for 3 days and was ultimately extubated.

Initially, the electrolyte derangements were attributed to ongoing diarrhea. Although the diarrhea resolved within 2 days of hospital presentation, the electrolyte imbalance persisted despite adequate replacement therapy and nasogastric tube feeding. As the patient had normal urine calcium, low blood calcium, elevated parathyroid hormone, and

Table 1. Laboratory result.

Parameters	Normal range	Values
Sodium	136–145 mmol/L	143 mmol/L
Potassium	3.4–4.5 mmol/L	2.2 mmol/L
Magnesium	1.6–2.6 mg/dL	0.5 mg/dL
Phosphorous	2.4–5.1 mg/dL	5.3 mg/dL
Chloride	98–107 mmol/L	99 mmol/L
Bicarbonate	20–31 mmol/L	26 mmol/L
Creatinine	0.50–0.80 mg/dL	1.47 mg/dL (baseline: 0.9 mg/dL)
Calcium	8.7–10.4 mg/dL	5.5 mg/dL
Albumin level	3.2–4.8 gm/dL	4.5 gm/dL
PTH	18.5–88 pg/mL	157.4 pg/mL
AGAP	5–15 mmol/L	14 mmol/L
Lipase	12–53 units/L	29 units/L
AST	0–33 units/L	37 units/L
ALT	10–49 units/l	16 units/L
Alkaline Phosphatase	46–116 units/L	49 units/L
Hemoglobin	11.0–14.5 gm/dL	12.1 gm/dL
WBC	4–10.8 K/uL	11 K/uL
HIV 1/2 Ab/Ag screen	–	Non- reactive
Clostridium difficile	–	Negative
Stool culture	–	Normal flora detected
Stool ova and parasite	–	No WBC/Ova/Parasite
Cryptosporidium antigen by DFA	–	Negative
Blood culture	–	Negative
Troponin	0–34 ng/L	14 ng/L
Vitamin B12 level	211–911 pg/mL	745 pg/mL
Vitamin D25 Hydroxy level	30–100 pg/mL	80.9 pg/mL
Urine analysis	–	Negative
Urine Calcium	0.5–35.7 mg/dL	5.1 mg/dL

AGAP: Anion gap, AST: Aspartate aminotransferase, ALT: Alanine transaminase, WBC: White blood cells, DFA: Direct Fluorescent antibody.

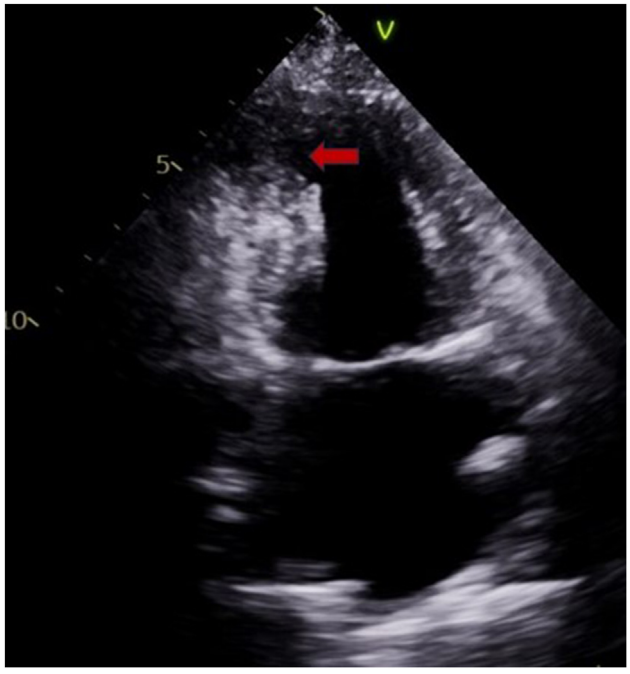

Fig. 1. Echocardiogram demonstrated moderately reduced left ventricular function (ejection fraction of 40%–45%) with a severely akinetic apical segment and apical ballooning (arrowhead).

phosphate level with the absence of vitamin D deficiency, we suspected PTH resistance as the likely cause of hypocalcemia and hypomagnesemia.

A repeat echocardiogram one week later, revealed a moderately decreased left ventricular ejection fraction ranging from 35% to 40%, along with multiple ventricular regional wall motion abnormalities suggestive of multivessel disease. A nuclear stress test showed no evidence of ischemia, with borderline normal global left ventricular function, indicating a likelihood of Takotsubo cardiomyopathy.

Pantoprazole was considered as the etiology of the electrolyte derangements and it was subsequently discontinued. One week after discontinuation, the patient's electrolyte levels normalized without the need for further replenishment. She was initiated on goal-directed medical therapy, including empagliflozin, lisinopril, metoprolol, and spironolactone. She was discharged with a follow-up plan for an echocardiogram in three months on an outpatient basis.

3. Discussion

There are currently six Food and Drug Administration approved PPIs: rabeprazole, lansoprazole, pantoprazole, esomeprazole, omeprazole, and dexlansoprazole.[1] The current indications for PPIs include the treatment of gastroesophageal reflux disease, non-steroidal anti-inflammatory drug and *Helicobacter pylori*-induced ulcers, duodenal ulcers, erosive esophagitis, and other pathological hypersecretory conditions, including Zollinger-Ellison syndrome.[6,7] It is also used for stress ulcer prophylaxis in critically ill patients and those at risk of developing gastrointestinal bleeding due to factors such as severe illness, major surgery, or critical injury. PPIs have demonstrated superior efficacy compared to H2RAs in the treatment of acid-related disorders, leading to the replacement of H2RAs.[8,9]

The common PPI associated adverse reactions are headache, nausea, stomachache, diarrhea, vomiting, and flatulence.[1] Occasional allergic reactions include rash, facial swelling, throat tightness, and difficulty breathing.[1] Recent data shows its association with myocardial infarction, *Clostridium difficile*, community-acquired pneumonia, bone fractures, subacute cutaneous lupus erythematosus, Alzheimer's dementia, and kidney injury.[10-13] One study shows the composite renal adverse drug reaction frequency for PPI to be 5.6% compared to 0.7% for H2RA monotherapy.[1] In 2011, the US FDA issued a warning highlighting the potential of long-term use of PPIs to reduce circulating magnesium levels, especially in patients concurrently taking other medications capable of causing magnesium depletion, such as diuretics.[2] It is now recommended that in patients using a PPI for an extended period (>2 weeks), serum magnesium levels be periodically monitored, particularly if prolonged PPI therapy is combined with drugs known to carry a risk of QT prolongation.[2] Pantoprazole and lansoprazole, in particular, can induce severe hypomagnesemia accompanied by hypokalemia and hypocalcemia.[5]

Magnesium promotes repolarization of myocardial cells by modulating rapid component of the delayed rectifier potassium current and transient outward current.[2] Additionally, it inhibits the long-lasting (L-type) calcium current, either through direct blockage of the L-type calcium channel pore or by modifying the activity of protein kinases or phosphoprotein phosphatases.[2] Potassium serves as the primary intracellular cation and functions to maintain osmolality and electroneutrality within the cell.[14] Calcium maintains cell wall integrity and cell permeability and is involved in intracellular energy production with its role in the formation of adenosine triphosphate.[14] In myocardial cells, calcium is essential for the actin-myosin cross-bridge necessary for contraction.

Electrolyte imbalance cardiomyopathy is an acquired condition characterized by diminished myocardial contractility and heart dilation in the absence of known causes like cardiac ischemia,

hypertension, rheumatic heart diseases, and congenital abnormalities. It excludes reversible factors such as alcohol, toxins, infection, and metabolic abnormalities.[14] Hypomagnesemia is hypothesized to cause takotsubo cardiomyopathy through various mechanisms, including the triggering of microvascular dysfunction and neurohormonal stress responses.[15] Additionally, it directly induces myocardial vasodilation, which can impact cardiac contractility.[15] The management involves ruling out acute coronary occlusion, addressing electrolyte imbalances, and avoiding any drugs that prolong the QT interval. Mild cases with rapid symptomatic improvement may not necessitate therapy; however, those with persistent left ventricular dysfunction may benefit from conventional heart failure treatments.[16]

Hypomagnesemia is an infrequent but potential cause of generalized tonic–clonic seizures and may go unnoticed when a patient presents with a seizure.[17] In cases of seizures or symptomatic/severe hypomagnesemia (<1.2 mg/dL, <1 mEq/L), it is recommended to administer 1–2 g of magnesium sulphate over a 5-min period, followed by an infusion of 1–2 g of magnesium sulphate per hour for the subsequent few hours.[4] If seizures persist, the bolus may be repeated, with continuous monitoring of potassium and magnesium levels during the therapy.[4] Since neurologic symptoms arising from electrolyte disorders are typically functional rather than structural, the manifestations are usually reversible. Long-term treatment with an anticonvulsant (AED) is not necessary as long as the underlying disturbance is rectified.[4,18] Additionally, AEDs alone are generally ineffective if the electrolyte disorder persists.[4,19]

While initiating the PPI, it is important to adhere to dosing and duration recommendations outlined by the FDA and American College of Gastroenterology.[1] Monitoring renal function and electrolytes, including potassium, calcium, magnesium, and sodium, is beneficial while the patient is on a PPI. Although H2RAs have demonstrated lower efficacy compared to PPIs, they might be considered as alternatives for patients at a high risk of developing renal and electrolyte imbalances.[1]

4. Conclusion

Increased awareness is necessary among clinicians when prescribing PPIs, as the safety profile of this drug class might not be as neutral as commonly believed. Given the strong relationship between electrolytes such as potassium, calcium, and magnesium with the cardiovascular system, central nervous system, and skeletal muscle, caution is warranted in the long-term use of PPIs due to their potential to cause electrolyte imbalances, leading to life-threatening arrhythmias, cardiomyopathy, and seizures.

Conflicts of interest

None.

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