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Torsade De Pointe Secondary to Proton Pump Inhibitor–Induced Hypomagnesemia

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Abstract **Case Report**

Magnesium is the third most common intracellular ion after potassium and calcium and plays an important role in several biochemical and physiological processes. Gastrointestinal disorders and kidney diseases are the main causes of hypomagnesemia, but it can also be an adverse effect of numerous drugs. Clinical manifestations of hypomagnesemia are nonspecific, the most severe of which are heart rhythm disturbances and mainly torsade de pointes. We present the case of an 82-year-old female patient presenting with torsade de pointes ventricular tachycardia secondary to proton pump inhibitor–induced hypomagnesemia.

Keywords: Hypomagnesemia, Proton pump inhibitors, Torsade de pointe.

INTRODUCTION

Magnesium is the third most common intracellular ion and represents an important cofactor during numerous enzymatic reactions. While hypomagnesemia is frequent in gastro-intestinal and renal disorders, its occurrence during the use of proton pump inhibitors (PPI) has also been described. Hypomagnesemia can be responsible of major complications, including heart rhythm disturbances. We present the case of an 82-year-old female patient presenting with torsade de pointes ventricular tachycardia secondary to proton pump inhibitor–induced hypomagnesemia

CASE REPORT

An 82-year-old female presented to the emergency department with extreme fatigue and anxiety. She also complained from shortness of breath but denied other cardiovascular or neuromuscular symptoms. Medical history included Hypertension, dyslipidemia and active smoking. Her medical therapy consisted in valsartan, hydrochlorothiazide, furosemide, atorvastatin and omeprazole on a daily basis. She did not report any alcohol consumption in the days preceding hospital admission.

Physical examination found a dehydrated patient, a slow heart rate of 50 beats per minute and a blood pressure of 100/70 mmHg. The rest of the physical examination was unremarkable. The electrocardiogram (ECG) showed sinus bradycardia with a corrected QT-interval of 520 ms. Transthoracic echocardiography was normal. The laboratory tests showed creatinine 252 µmol/L (N: 45–90 µmol/L), urea 9.1 mmol/L (N: 2.6–6.4 mmol/L), estimated glomerular filtration rate (eGFR) 17 mL/min/1.73 m² (N: >30 mL/min/1.73 m2), sodium 138 mmol/L (N: 136–145 mmol/L), potassium 3.5 mmol/L (N: 3.5–5.1 mmol/L), calcium 2.1 mmol/L (N: 2.1–2.55 mmol/L). Ultrasound of the kidneys did not show any signs of chronic kidney disease.

At this point, the diagnosis of acute renal failure secondary to dehydration was made but three hours later, the patient presented severe convulsions and the ECG showed Torsade de pointes (Tdp) ventricular tachycardia. A continuous infusion of magnesium at a rate of 3-10 mg/min terminated the arrhythmia. Severe hypomagnesemia was diagnosed with magnesium level at 0.23 mmol/L (references: 0.7–1.1 mmol/L). It was concluded that the diuretic treatment was responsible of the severe hypomagnesemia causing the arrhythmia. After interruption of diuretics and correction of electrolyte disturbances, marked improvement of the clinical condition and the renal function was noted.

During the outpatient check-up, three months later, the patient again presented with the same complaints accompanied by hypomagnesemia at 0.42 mmol / l despite a normal renal function. A thorough

examination could not detect any gastrointestinal or renal cause of hypomagnesemia. The conclusion was that the hypomagnesemia was a side effect of the proton pump inhibitor (PPI) treatment. Omeprazole was stopped, and 6 months later, serum magnesium levels are currently normal and stable.

DISCUSSION

Magnesium is the third most common intracellular ion after potassium and calcium and plays an important role in several biochemical and physiological processes [1-3]. Its functions in the body include the regulation of protein synthesis, muscle and nerve transmission, neuromuscular conduction, signal transduction, blood glucose control, and blood pressure regulation [4, 5].

Gastrointestinal disorders and kidney diseases are the main causes of hypomagnesemia, but it can also be a side effect of several drugs among of which PPIs. A number of studies suggest that PPIs alter the function of magnesium molecular transporters impairing its intestinal absorption; probably influenced by a complicated interplay of molecular biology, pharmacology and genetic predisposition [6].

Symptoms of hypomagnesemia typically begin to manifest at serum levels <0.66 mmol/L (1.6 mg/dl) [7] and mainly depend on the rate of development rather than the actual serum magnesium concentration. Clinical manifestations include weakness, fatigue, increased neuromuscular excitability (muscle fasciculation, cramps, tremor carpopedal spasms, numbness of the hands and tetany), central nervous system disorders (lethargy, drowsiness, depression and generalized convulsions), and cardiac manifestations (the most severe of which are ventricular rhythm disorders such as torsade de pointes).

Torsade de pointes is a life-threatening polymorphic ventricular tachycardia characterized by a continuous twisting of the QRS axis around an imaginary baseline, which if left untreated will degenerate into ventricular fibrillation and sudden death [8]. In the case of hypomagnesemia, TdP is explained by the loss of magnesium's modulating effects on several potassium channels responsible of the repolarization of myocardial cells [9, 10]. In addition, extra-cellular magnesium exerts an important anti-arrhythmic action by stabilizing the cardiac membrane through a direct block of the L-type calcium channel or via modification of the activity of protein kinases or phosphoprotein phosphatases [11].

Epstein *et al.*, [12] first reported proton pump inhibitor-induced hypomagnesemia in 2006, and since then many more studies observed the same adverse effect of PPIs [13-17] and several others accompanied by serious cardiac arrhythmias including TdP [18-22]. Lazzerini *et al.*, [18] reported 48 patients with hypomagnesemia and TdP, of which 28 (58%) were on PPI treatment and 20 (42%) were not. Patients with PPI treatment had lower serum magnesium levels compared to those without PPI treatment (1.60 vs 1.84 mg/dl, p = 0.03). The corrected QT was prolonged in both groups, but was longer in patients taking PPIs. Both groups were very similar in terms of concomitant cardiovascular diseases. Another study included 421 patients admitted to the critical care unit with unstable angina, non-ST elevation myocardial infarction and cardiac arrhythmias, of whom 184 (43.8%) were on PPI treatment. Magnesium levels were low (<1.8 mg/dl) in 95 patients (22.5%) and 167 patients (39.6%) developed cardiac arrhythmias. The authors found a significant association of PPI use with the incidence of hypomagnesemia and cardiac arrhythmias [19].

Serum magnesium levels should be measured before PPI prescription and monitored periodically thereafter, especially in patients taking concomitant drugs that induce magnesium deficiency, such as diuretics [23]. PPI treatment should be discontinued if hypomagnesemia occurs, and for patients who require treatment for peptic ulcer disease or gastroesophageal reflux disease, H2 receptor antagonists could substitute PPIs, since these drugs do not impair magnesium absorption [23].

CONCLUSION

Proton pump inhibitor-induced hypomagnesemia can cause life-threatening ventricular arrhythmias. Magnesium levels should be carefully monitored in patients taking PPIs especially with concomitant drugs such as diuretics.

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