Clinical Case Study

Woman with Hypomagnesemia and Hypocalcemia

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CASE DESCRIPTION

A 71-year-old woman was referred to the endocrinology clinic after several years of unresolved hypomagnesemia that required numerous hospital admissions to receive intravenous magnesium. She previously presented with palpitations on 3 occasions, and once with diarrhea and vomiting. The blood tests on all 4 presentations demonstrated severe hypomagnesemia (Table 1).

Her medical history included type 2 diabetes mellitus and hiatal hernia. Her regular medications included simvastatin, esomeprazole, verapamil, pioglitazone, gliclazide, metformin, and calcium, magnesium, and vitamin D supplementation. Clinical examination in the endocrinology clinic was unremarkable, and no abnormality was demonstrated on electrocardiogram. An echocardiogram was normal.

Laboratory results at this visit included serum magnesium 0.52 mg/dL (0.21 mmol/L) [reference interval 1.7–2.4 mg/dL (0.7–1.0 mmol/L)] and serum calcium 6.84 mg/dL (1.71 mmol/L) [reference interval 8.8–10.6 mg/dL (2.20–2.65 mmol/L)]. Serum albumin was 35 g/L (reference interval 35–52 g/L). The results of her other biochemical tests were unremarkable. Twenty-four-hour urine magnesium excretion was undetectable [reference interval 0.5–1.2 mg/dL (0.2–5.0 mmol/24 h)], as was random urine magnesium [<0.25 mg/dL (<0.1 mmol/L)]. Intact parathyroid hormone (PTH)3 was 20 ng/L (reference interval 15–88 ng/L), inappropriately low in the presence of hypocalcemia. All analytes were measured with a Beckman Olympus AU2700 general chemistry analyzer with the exception of intact PTH, which was measured with a Beckman Coulter Access II.

The patient gave full written consent for the use of her clinical information and laboratory tests for the purposes of a case report in the medical literature.

QUESTIONS TO CONSIDER

1. What are the common causes of hypomagnesemia?
2. Are any of the patient’s medications potential causes of hypomagnesemia?
3. What effect does magnesium have on calcium and parathyroid hormone?

DISCUSSION

The patient was advised to stop esomeprazole and was prescribed ranitidine for dyspepsia. After cessation of esomeprazole, serum magnesium, calcium, and phosphate recovered to within reference concentrations. The patient was diagnosed with proton pump inhibitor–induced hypomagnesemia (PPIH) with secondary hypoparathyroidism.

The causes of hypomagnesemia are commonly classified according to either a renal or gastrointestinal origin (1). Causes of renal loss of magnesium include medication (most commonly diuretics, cisplatin, aminoglycosides, and cyclosporine); renal infection (pyelonephritis, glomerulonephritis); congenital tubulopathy (Gitelman syndrome); and osmotic diuresis. Causes of gastrointestinal loss of magnesium include diarrhea and vomiting and abuse of laxatives. Hypomagnesemia can also be due to lack of intake or absorption of dietary magnesium, due to malabsorption, bowel resection, fistula, malnutrition, alcoholism, or total parenteral nutrition (1). In neonates, low serum magnesium can be due to primary intestinal hypomagnesemia, an inherited metabolic disorder. This condition presents early in life (1). Mild hypomagnesemia is frequently observed in hospital inpatients; possible causes include poor nutrition, use of parenteral feeding, and use of diuretics and aminoglycosides (1). Hypomagnesemia leads to secondary hypoparathyroidism through a combination of impaired PTH secretion and end-target resistance (2).

Renal loss of magnesium was excluded in this patient by demonstrating undetectable urine magnesium in the presence of hypomagnesemia; this indicated appropriate maximal renal reabsorption of magnesium. Although the patient was admitted for an episode of diarrhea and vomiting, loss of magnesium through this mechanism was excluded owing to the short duration of illness and the chronic hypomagnesemia despite improvement of
these symptoms. A thorough history and clinical examination excluded the most common nonrenal causes of hypomagnesemia. The hypomagnesemia resolved when esomeprazole was stopped and switched to ranitidine, indicating that the cause of the condition was PPIH.

Magnesium is absorbed from the diet via passive and active processes: passive intercellular movement of magnesium through enterocyte junctions of the intestinal epithelium, and receptor-mediated active transport of magnesium into enterocytes via the transient receptor potential melastatin (TRPM)-6 and TRPM-7 transporters (3). These transporters are expressed in the apical membranes of enterocytes; TRPM-6 is also expressed in the apical membrane of the distal convoluted tubule and is involved in magnesium reabsorption (3).

PPIH was first described in 2006 (4). A systematic review of the literature found 36 reported cases (5), and the clear association between PPI and hypomagnesemia in the community was recently demonstrated in a cohort of approximately 95,000 patients (6). The majority of the 36 cases presented with symptoms of hypomagnesemia, such as seizures, dizziness, nausea, paresthesia, vomiting and diarrhea, muscle cramps, and tetany; some cases also demonstrated cardiac arrhythmia (6). In this case, the patient presented with palpitations. She was subsequently diagnosed with an atrioventricular nodal reentrant tachycardia. Her symptoms of palpitations partially resolved after magnesium replacement but were completely cured after cardiac ablation therapy. A causal relationship between her hypomagnesemia and cardiac arrhythmia remains unclear, although it can be speculated that the hypomagnesemia provided the trigger and unmasked the cardiac conduction defect.

Magnesium has complex effects on several cardiac ion channels. Consequently, hypomagnesemia can predispose to atrial and ventricular ectopic activity, atrial and supraventricular tachyarrhythmias, including atrial fibrillation, and ventricular tachyarrhythmias (7, 8). With the increasing use of anticoagulation in the management of paroxysmal, persistent, and permanent atrial fibrillation with the concomitant prescribing of proton pump inhibitors, inadvertent hypomagnesemia may predispose to further episodes of atrial fibrillation and other arrhythmias (7, 8).

The patient did not present with any of the other signs or symptoms reported in other previously reported cases and remained unusually normokalemic. The median number of years of PPI use before the onset of hypomagnesemia in the reported cases was 5.5 years; in this case, the patient was first discovered to have hypomagnesemia 2 years after the prescription of esomeprazole.

The exact mechanism of PPIH is unknown. Proposed mechanisms include disruption of the TRPM-6/7–mediated active transport of dietary magnesium across the apical membrane of the intestine due to a decrease in the luminal hydrogen ion concentration as a result of proton pump inhibition, or impaired passive magnesium absorption across the intercellular junctions (3). Questions still remain as to whether the mechanism of PPIH is pH dependent or independent, and whether PPIH affects passive and/or active transport of intestinal magnesium. TRPM-6/7 disruption is thought to be due to a change in affinity for magnesium after pH-induced alterations to the TRPM-6/7 active binding site (3). However, the major route of intestinal magnesium absorption is via the passive process, which may indicate that impaired passive absorption leads to the profound hypomagnesemia demonstrated in this case. In this case, and in all reported cases, hypomagnesemia was resolved by switching the patient from a PPI to an H2 receptor antagonist such as ranitidine, which provides further support toward a pH-independent cause of hypomagnesemia.

Despite the widespread prescription and use of PPIs since the late 1980s, PPIH has rarely been described in the literature, and cases have been described only since 2006 for several possible reasons: most reported cases were long-term users of PPIs (with a median use of 5.5 years); mild hypomagnesemia may be asymptomatic; and serum magnesium concentrations are rarely requested for patients in a primary care setting, unless there is reflex testing for magnesium (9). Alternatively, PPIH may be a
rare side effect of long-term PPI use affecting only susceptible individuals. The U.K. Medicines and Healthcare Products Regulatory Agency Drug Safety Update recommends obtaining baseline serum magnesium on new patients started on PPIs and regular monitoring of patients on long-term PPI treatment (10, 11).

CONCLUSIONS

A case of PPIH and secondary hypoparathyroidism has been described. PPIH, hypocalcemia, and secondary hypoparathyroidism resolved after ceasing esomeprazole and switching the patient to ranitidine. The exact mechanism of PPIH is still unknown but may be based on either the disruption of TRPM-6/7–mediated active transport or passive absorption of intestinal magnesium. Hypomagnesemia has complex effects on cardiac ion channels and can predispose to a number of arrhythmias, especially in patients with predisposing cardiac conditions.

POINTS TO REMEMBER

- Low serum magnesium results should be investigated when first discovered.
- Guidelines recommend obtaining baseline serum magnesium on new patients started on PPIs and regular monitoring of patients on long-term PPIs.
- Consider drug history when investigating hypomagnesemia.
- Consider hypomagnesemia when investigating hypocalcemia and hypoparathyroidism.

Commentary

Mark A. Perazella*

Proton pump inhibitors (PPIs) are one of the most widely used medications to treat acid-related gastrointestinal disease. Although they are generally safe, hypomagnesemia is an adverse effect confirmed in numerous case reports/series and observational studies. In contrast to most drug-related causes of hypomagnesemia, the source of magnesium wasting with PPIs is gastrointestinal rather than renal. Gastrointestinal magnesium absorption occurs via passive paracellular diffusion and active transport via apical membrane magnesium channels (TRPM-6/7) in enterocytes. The gut absorbs magnesium, and the kidneys regulate its excretion via TRPM-6 magnesium channel reabsorption in distal tubules. Because intracellular magnesium is a cofactor for enzymatic reactions and is critical in energy metabolism, the body is poised to prevent deficiency.

The current case is an extreme example of this PPI-related adverse effect. The reader should appreciate that hypomagnesemia is a relatively rare complication given the extent of PPI use. PPIs do not cause hypomagnesemia of magnesium wasting with PPIs.