Endocrinol Nutr. 2011;58(10):550–555

ENDOCRINOLOGÍA Y NUTRICIÓN

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SCIENTIFIC LETTERS

Hypomagnesemia induced by proton pump inhibitors, diarrhea, and lactose intolerance☆

Hipomagnesemia relacionada con el uso de inhibidores de la bomba de protones, diarrea e intolerancia a lactosa

Sir,

Hypomagnesemia is an uncommon biochemical change in outpatients, but may be detected in up to 12% of hospitalized patients, in whom factors such as total and enteral nutrition, diuretic use, diarrhea, hypoalbuminemia, and nephrotoxic drugs (antibiotics, chemotherapeutic, etc.) play a significant role in its occurrence. Symptoms related to hypomagnesemia usually occur with serum magnesium levels lower than 1.2 mg/dL. The condition is very frequently associated with the presence of hypocalcemia, hypokalemia, and metabolic alkalosis. Different authors have recently reported several cases of symptomatic hypomagnesemia associated with long-term use of proton pump inhibitors (PPIs).

A 39-year-old Caucasian male attended the emergency room reporting cramps in the hands and feet and numbness in the face for the previous 24 h. He had experienced similar episodes during the previous 4 years, which he associated with abundant diarrheal stools. The patient had hypertension, dyslipidemia, and a hiatal hernia. 5 years before, he had also suffered a right hemispheric cerebral infarction of a cardioembolic origin from which he recovered without sequelae. Since then, he had been receiving the following treatment: acenocoumarol 3 mg daily, acetylsalicylic acid 100 mg daily, atenolol 25 mg every 12 h, amlodipine 5 mg daily, losartan potassium 50 mg daily, hydrochlorothiazide 25 mg daily, simvastatin 20 mg daily, and omeprazole 40 mg daily. He had not taken alcohol, herbal products, laxatives, or nephrotoxic drugs.

Upon arrival at the emergency room he had blood pressure of 118/62 mmHg, heart rate of 103 bpm, was eupneic with a basal oxygen saturation of 97%, and had no fever. Muscle twitching was found in the quadriceps muscles, and carpopedal spasm in the hands and feet. Chvostek and Trosseau signs were negative. Pulmonary, cardiac, and abdominal examinations were all normal. Laboratory test results included: creatinine 1.01 mg/dL, urea 26 mg/dL, Na^+ 142 mM/L, Cl^- 102 mM/L, K^+ 2.2 mM/L (3.5–5.5 mequiv./L), Ca^{++} 6.87 mg/dL (8.7–10.3 mg/dL), Mg^{++} 0.7 mg/dL (1.40–2.40 mg/dL), P^+ 1.8 mg/dL (2.7–4.5 mg/dL). Venous blood gases included pH 7.45, pCO_2 43 mmHg, and HCO_3^- 29.9 mequiv./L. An electrocardiogram showed sinus rhythm with no ST and/or QTc changes. Chest and abdominal X-rays were normal. The patient was admitted to the endocrinology ward and intravenous replacement therapy with Mg^{++}, K^+ and Ca^{++} was urgently started in accordance with the established recommendations (4 ampoules of Mg^{++} 12 mequiv. in 1000 mL of 5% glucose solution in 24 h, a 20 mequiv./L KCl solution at a maximum rate of 10 mequiv./h, and a load of 200 mg elemental Ca^{++} followed by infusion at 2 mg/kg/h). Laboratory tests were performed every 3 h for electrolyte adjustment. After a few hours of treatment, the electrolytes normalized and the symptoms were resolved. Oral supplements of Ca^{++}, Mg^{++}, and K^+ continued to be administered.

In laboratory tests performed in the 2 years prior to admission there were no Mg^{++} or P^+ values recorded, and hypocalcemia (7.4; 8.4; 8.5) and hypokalemia (3.5; 2.2; 3.3) were the only noteworthy findings.

Tests for renal tubular disease, thyroid function, bone metabolism (PTH 35.8 pg/mL, vitamin D 25-OH 38.10 ng/mL), and hyperaldosteronism were normal. The patient was discharged home with no symptoms 10 days after admission. The thiazide was discontinued, and treatment was continued with oral supplements of Mg^{++} (4.25 mmol/day) and Ca^{++} (1000 mg/day). Three months later, the patient returned to the endocrinology outpatient clinic for a scheduled visit with the same symptoms. This time, laboratory test results included K^+ 3.5 mM/L, total Ca^{++} 8.2 mg/dL, P^+ 2.8 g/dL, and Mg^{++} 1.10 mg/dL. Gastrointestinal study was completed with functional tests, computed tomography of the chest and abdomen, colonoscopy, oral panendoscopy, and gastrointestinal transit to rule out malabsorptive or paraneoplastic syndromes.

☆ Please cite this article as: Cano Megías M, et al. Hipomagnesemia relacionada con el uso de inhibidores de la bomba de protones, diarrea e intolerancia a lactosa. Endocrinol Nutr. 2011;58:550–5.

2173-5093/$ – see front matter

Table 1 Summary of reported cases: clinical symptoms, electrolyte changes, treatment, and score in the Naranjo scale.

Article	Sex/age	Drug, daily dose, duration (years)	Symptoms	Electrolyte (mg/dL)	25-OH vitD/PTH	Remarks	Naranjo scale	Recovery (weeks)
Epstein et al. (2006)	F/51 M/80	Omeprazole (20 mg/12 h). 12 years Omeprazole (20 mg/day). Several years	Carpopedal spasm Carpopedal spasm	Mg^{++} 1.05 Ca^{++} 7.37 Mg^{++} 0.48 Ca^{++} 6.33	Normal/low Normal/low	After esomeprazole, low Mg^{++} levels	Probable Probable	Yes (56 weeks) Yes (40 weeks)
Cundy et al. (2008)	M/67 F/63	Omeprazole (20 mg/day). 12 years Omeprazole (40 mg/day). 6 years	Generalized seizures Generalized seizures	Mg^{++} 0.28–1.03 Ca^{++} 6.12–8 Mg^{++} 0.48–0.52 Ca^{++} 7.08	ND/low ND/low	After esomeprazole, low Mg^{++} levels	Probable Probable	Not specified Not specified
Shabajee et al. (2008)	M/81 F/78	Omeprazole (40 mg/day). Not determined. Omeprazole (40 mg/day). 7 years	Cramps, paresthesia, atrial flutter; A-V block Paresthesia. Tetany	Mg^{++} 0.45 Ca^{++} 5.83 K^{+} 2.9 Mg^{++} 0.24 Ca^{++} 6.25 K^{+} 2.7 P^{+} 1.178	ND/normal ND/ND	Vomiting Vomiting, diarrhea, loop diuretics	Probable Probable	Yes (1–3 weeks) Yes (1–3 weeks)
Francois et al. (2008)	F/62	Omeprazole (20 mg/12 h). 2 years Esomeprazole (40 mg/day). 1 year	Acute tetraparesis	Mg^{++} 0.768 Ca^{++} 6.04	Normal/low	Intestinal giardiasis	Possible	Yes (4–8 weeks)
Broeren et al. (2009)	M/58	Omeprazole (40 mg/day). 8 years	Loss of consciousness. Seizures	Mg^{++} 0.38 Ca^{++} 6.87 K^{+} 2.7	ND/low	Electrolyte changes after lansoprazole and pantoprazole	Probable	Not specified
Kupiers et al. (2009)	M/76	Esomeprazole (40 mg/day). 1 year	Lethargy. Cramps	Mg^{++} 0.43 Ca^{++} 5.25 K^{+} 3.3	Normal/low	After esomeprazole, low Mg^{++} levels	Probable	Yes (6 weeks)
Gato Díez et al. (2011)	M/70	Omeprazole (20–40 mg/day). 11 years	Supraventricular tachycardia. Tetany	Mg^{++} 0.48 Ca^{++} 7.08	Normal/normal	Giardiasis	Probable	Yes (4–6 weeks)