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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.

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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)

Table 1 (*Continued*)

Article	Sex/age	Drug, daily dose, duration (years)	Symptoms	Electrolyte (mg/dL)	25-OH vitD/PTH	Remarks	Naranjo scale	Recovery (weeks)
Hoorn et al. (2010)	M/63 F/73 F/62 M/81	Esomeprazole (20 mg/day). 11 years Pantoprazole (40 mg/day). 1 year Omeprazole (40 mg/day). 13 years Esomeprazole (20 mg/day). 3 years	Atrial fibrillation U waves Prolonged QTc. ST decrease Prolonged QT	Mg^{++} 0.06–1.88 Ca^{++} 7.8 K^{+} 2.8 Mg^{++} 0.68–1.68 Ca^{++} 11.5 * K^{+} 2.8 Mg^{++} <0.16–1.8 Ca^{++} 7.1 K^{+} 2.7 Mg^{++} 0.26–1.58 Ca^{++} 4.44 K^{+} 3	Low/normal Low/normal Normal/normal Normal/normal	Loss of consciousness Sarcoidosis Primary hyperparathyroidism Prior intestinal giardiasis. Lymphangiectasis. Rabeprazole	Probable Probable Probable Probable	Yes (2 weeks) Yes (12 weeks) Yes (2 weeks) Yes (3 weeks)
MacKay and Bladon[a] (2010)	9F:1M/68.8 (±8.6)	Esomeprazole, omeprazole, pantoprazole 8.3 (±3.5) years	Paresthesia (n=5). Cramps (n=3). Dizziness (n=5). Weakness (n=6). Tetany (n=2). Loss of consciousness (n=3)	Mg^{++} 0.63 Ca^{++} 7.49	Low 2/4 cases tested/ Abnormally low in 2	Concomitant diuretic use (n=8). *Campylobacter* enteritis (n=1)	Possible/ probable	Yes (mean, 2 weeks)
Cano Megías et al. (2011)	M/40	Omeprazole (40 mg/day) 5 years	Cramps. Tetany. Paresthesia	Mg^{++} 0.7 Ca^{++} 7.6 K^{+} 2.2 P^{+} 1.8	ND/normal	Concomitant thiazide use. Diarrhea. Lactose intolerance	Probable	Yes (3 weeks)

F: female; ND: not done; M: male.

[a] Mean values of a series of 10 patients. The Naranjo scale could only be applied to the single case reported, giving a score of probable. The Naranjo scale is one of the algorithms most commonly used to assess the causal relationship of a drug adverse reaction (DAR). (Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45. The categories corresponding to the total score are as follows: DAR is: definite: > 9; probable: 5–8; possible: 1–4; unlikely <1.

The only change found in all of these tests was a positive lactose intolerance test. Despite oral supplements of Ca^{++} and Mg^{++}, hypomagnesemia and hypocalcemia persisted until omeprazole was discontinued and ranitidine 150 mg every 12 h was started. Oral magnesium salts and a lactose-free diet were maintained upon discharge. After 3 weeks, tests showed normalization of the electrolyte parameters. Oral supplements were discontinued, and there were no subsequent decreases in serum levels of Mg^{++} and Ca^{++}.

The exact incidence of this side effect of PPIs is currently unknown. A search in Pub Med/MEDLINE for recently published articles (2002–January 2011) using the terms *hypomagnesemia*, *proton pump-inhibitor* and/or *omeprazole*, *pantoprazole*, *lansoprazole*, found up to 25 published cases (including the one reported here). Table 1 summarizes the type of PPI, treatment dosage and duration, clinical characteristics, precipitating factors, therapeutic management, and prognosis in the reported cases. All patients had been treated with PPIs for at least 1 year (mean, 7.7 years; range, 1–13). There is a female sex predominance in the reported series (15 females, 10 males) which may be attributed to better treatment compliance.[1] Mean age at occurrence of the condition was 67.9 years (range, 40–81 years). Hypomagnesemia is not only associated with omeprazole[1] (n=15), but appears to be a drug-class side effect (esomeprazole,[1–4] pantoprazole,[1] lansoprazole,[1,5] and rabeprazole[4]). In addition, the risk of hypomagnesemia is not dose-dependent. It may occur with both low or middle doses (20–40 mg/day) and with 1 or 2 daily doses.[2,6,7] Most patients (n=21, 84%) had neuromuscular signs such as weakness, dizziness, paresthesia,[1] muscle cramps,[8] carpopedal spasm,[2] generalized seizures,[2,5] and even loss of consciousness or acute tetraparesis.[3] Three of these patients also had electrocardiographic changes including Supraventricular tachycardia,[7] atrial flutter,[8] and atrial fibrillation.[4] Hoom et al.[4] only reported cardiac rhythm disorders with no associated neuromuscular symptoms. Approximately one-fourth of all patients (n=6, 24% of the total) had no electrocardiographic changes. Triggering factors contributing to hypomagnesemia are frequently reported (Table 1). The triggering factors in the case reported here were chronic use of thiazide diuretics and diarrhea due to lactose intolerance, both of them known causes of hypomagnesemia from renal and gastrointestinal losses.

Cases published in the medical literature report the concomitant occurrence of other electrolyte disorders such as hypokalemia (n=9, mean value 2.7 mM/L) and hypophosphatemia (n=2).[5,8] Secondary hypocalcemia was reported in all cases (mean Ca^{2+} values, 7.16 mg/dL).

The mechanism of hypomagnesemia induced by PPIs has not yet been elucidated. Schlingman et al.[9] proposed that treatment with PPIs induced changes in intestinal pH and caused a decreased expression of the family of transient receptor potential melastatin (TRPM) channels in heterozygous individuals. Two of these receptors, TRPM6 and TRPM7,[9,10] which are essential for intestinal transepithelial and renal tubular transports of Mg^{++}, have recently been identified. Their expression is regulated by several factors including Mg^{++} serum levels, angiotensin II, aldosterone, bradykinin, estrogens, drugs inducing hyperglycemia, diabetes mellitus, diuretics, acidosis or alkalosis, or immunosuppressants such as tacrolimus.

Complete recovery from water and electrolyte disorders usually occurred after a mean of 6 weeks (1–56 weeks). In almost two thirds of the patients (n=18), the PPI was replaced by an anti-H_2, while drug discontinuation was the only action taken in the remainder. In conclusion, hypomagnesemia induced by long-term treatment with PPIs is a drug-class side effect. It may be triggered by multiple factors, which should be considered in each individual patient. MacKay and Bladon[1] recommended annual electrolyte tests, including K^+, Ca^{++}, and Mg^{++}, in all patients treated with PPIs. Hypomagnesemia is an electrolyte change fully reversible upon PPI discontinuation. However, most patients require several weeks of treatment with oral Mg^{++} and Ca^{++} supplements for complete resolution of electrolyte abnormalities. Clinicians should be aware of potential electrolyte changes in patients attending with tetany, arrhythmia, or seizures for an unknown cause and who are taking long-term treatment with PPIs.

Conflicts of interest

The authors state that they have no conflicts of interest.

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References

1. MacKay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. QJM. 2010;103:387–95.
2. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Eng J Med. 2006;335:1834.
3. Francois M, Lévy-Bohbot N, Caron J, Durlach V. Chronic use of proton-pump inhibitors associated with giardiasis: a rare case of hypomagnesemic hypoparathyroidism? Ann d'Endocrinol. 2008;69:446–8.
4. Hoorn EJ, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis. 2010;56:112–6.
5. Broeren MAC, Geerdink EAM, Vader HL, van den Wall Bake AWL. Hypomagnesaemia induced by several proton-pump inhibitors. Ann Inter Med. 2009;151:755–6.
6. Cundy T, Dissanayake A. Severe hypomagnesaemia in long-term users of proton-pump inhibitors. Clin Endocrinol (Oxf). 2008;69:338–41.
7. Gato Díez A, Córdoba Soriano JG, Mora Escudero I. Severe hypomagnesaemia due to long-term treatment with omeprazole. Med Clin (Barc). 2011;136:84–5.
8. Shabajee N, Lamb EJ, Sturgess I, Sumathipala RW. Omeprazole and refractory hypomagnesaemia. BMJ. 2008:337–425.
9. Schlingmann KP, Waldegger S, Konrad M, Chubanov V, Gudermann T. TRPM6 and TRPM7-gatekeepers oh human magnesium metabolism. Biochim Biophys Acta (BBA). 2007;1772:813–21.

10. Kupiers MT, Thang HD, Arntzenius AB. Hypomagnesaemia due to use of proton pump inhibitors—a review. Neth J Med. 2009;67:169–72.

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Tumor-related gynecomastia☆

Ginecomastia de origen tumoral

Gynecomastia is defined as a benign proliferation of breast tissue in males and results from an imbalance between estrogenic and androgenic activities.[1] It may be due to decreased androgen production, and increased estrogen production, or an increased peripheral conversion of androgenic precursors. Other potential mechanisms include the blockade of androgenic receptors and increased androgen binding to its transporter protein (SHBG).[2]

Its less common causes include testicular tumors, which account for approximately 2% of cases of gynecomastia.[3] We report a case of gynecomastia secondary to production of chorionic gonadotropin (HCG) by a testicular germ cell tumor.

A 27-year-old male patient with an unremarkable history except for a septoplasty procedure and who smoked 10 cigarettes daily attended the clinic for painful bilateral gynecomastia over the previous three months. He reported no associated clinical signs of hypogonadism, body weight changes, use of drugs or cosmetic products, nor illegal drug consumption. His family history was unremarkable.

Physical examination revealed a normal male phenotype, with adequate body hair distribution. Weight was 71.7 kg and height 1.71 cm (body mass index 25 kg/m^2), and blood pressure was normal (130/80 mmHg). A bilateral, grade II, symmetrical increase in glandular breast tissue was palpated, with no nodules and no secretion on expression. No goiter was palpated, and cardiopulmonary auscultation was normal. The abdomen was soft and amenable to pressure, with no masses or visceromegalies. Both testes were inside the scrotum, with volumes of 25 mL and 15–20 mL for the right and left testis, respectively. No testicular masses were palpated.

Based on this recent onset of bilateral gynecomastia with no identifiable cause, laboratory tests were requested and showed the following values: HCG 27,703 IU/L (normal less than 2.5 IU/L), LH 16.2 IU/L (normal 0.87–7.6), FSH less than 0.1 IU/L (normal 0.7–11.1); estradiol 143 ng/L (normal 0–80); free testosterone 53 ng/L (normal 8.8–27). Results of all other general laboratory parameters and thyroid hormone and alpha-fetoprotein levels were normal. A testicular ultrasound examination reported a normal right testis and a left testis with diffuse hypoechogenicity, with multiple scattered hyperechogenic images related to microlithiasis. A 6-mm hypoechoic area with ill-defined margins was seen in the middle part of the left testis (Fig. 1). Dilatation of left pampiniform plexus related to varicocele. Chest X-rays were normal.

The patient was referred to urology, where left transinguinal orchiectomy plus placement of testicular prosthesis were successfully performed. A CT scan of the chest, abdomen, and pelvis showed no adenopathies of lesions suggesting metastatic disease.

The pathological report described a burned-out testicular tumor associated with intratubular germ neoplasm with a lesion-free surgical margin. There was a whitish area consistent with scar tissue together with a granulomatous lesion with heavy histiocyte reaction, with no residual tumor cells. Therefore, a definitive pathological diagnosis was not possible. There was no apparent vascular infiltration. There was Leydig cell hyperplasia and intratubular stones.

In laboratory tests performed after surgery, HCG concentrations continued to be high (83,117 IU/L). Chemotherapy was therefore decided upon at a multidisciplinary session. The patient lived in another region and said that he would rather continue treatment in his home town. His reference hospital was therefore contacted for transfer.

Gynecomastia results from an imbalance between estrogens and androgens. Physiological gynecomastia is very

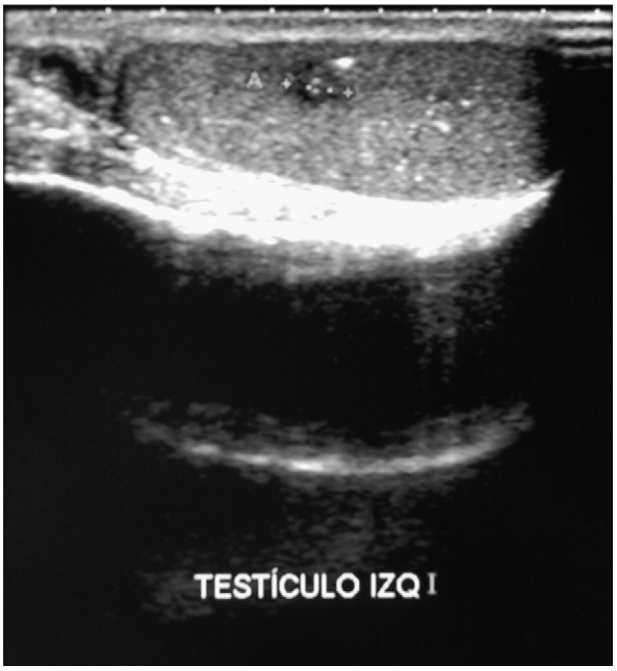

Figure 1 Testicular ultrasound showing a hypoechoic lesion with irregular margins in left testis, and images consistent with scattered microlithiases.

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