

Case report

Hypomagnesaemia and hypocalcaemia in a patient with systemic sclerosis: role of proton pump inhibitors

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ABSTRACT

Proton pump inhibitors (PPI) are widely used in patients with systemic sclerosis (SSc) due to the chronic gastroesophageal reflux. The authors report a female patient with a 9-year history of SSc and long-term use of omeprazole, who complained of paresthesia and asthenia for 12 months. Physical examination revealed clinical signs of hypocalcaemia confirmed by laboratory tests that also showed hypomagnesaemia. After exclusion of possible causes, hypomagnesaemia secondary to PPI was diagnosed and omeprazole was replaced by a histamine H₂-receptor antagonist: ranitidine. Despite continuous magnesium supplementation, the reintroduction of PPI at a lower dose due to worsening of dyspeptic symptoms led to recurrence of hypomagnesaemia. After definitive suspension of PPI, reintroduction of ranitidine and optimisation of anti-reflux environmental measures, the patient stabilised. In conclusion, SSc patients using PPIs should have their magnesium and calcium serum levels measured periodically, and non-specific symptoms such as asthenia, generalised paresthesia or life-threatening manifestations (seizures, arrhythmias) should not be neglected.

Introduction

Chronic gastroesophageal reflux (GER) observed in systemic sclerosis (SSc) can lead to Barrett's oesophagus, increasing the risk to develop an oesophageal adenocarcinoma (1), and is also associated with interstitial lung disease (2). Proton pump inhibitors (PPI) are widely used in patients with SSc due to the high prevalence of esophageal dysmotility and GER (3, 4).

Hypomagnesaemia is a rare complication of PPI and usually occurs in indi-

viduals with chronic long-term use of these drugs (5). Overall, PPI associated hypomagnesaemia can be symptomatic and cause paresthesias, seizures and arrhythmias (6). In most cases, oral and/or intravenous magnesium replacement is not sufficient and PPI must be discontinued (7).

The possible association between symptomatic hypomagnesaemia and SSc was previously described in a recent publication, in which many hypotheses were proposed (8). We report a case of a patient with SSc and symptomatic hypomagnesaemia that was clearly associated to the chronic use of omeprazole.

Case report

A 79-year-old female patient with a 9-year history of SSc presented in our outpatient clinic complaining of paresthesia and asthenia for 12 months. She referred chronic use of omeprazole 80mg/day.

Physical examination revealed the presence of clinical signs of hypocalcaemia (positive Chvostek's and Trousseau's signs), and she was hospitalised for investigation.

Laboratory tests showed high-titer positive antinuclear antibodies (nucleolar pattern) and negative specific SSc auto-antibodies and also confirmed the clinical suspicion of hypocalcaemia associated with hypomagnesaemia and hypocalciuria. Laboratory exams are shown in Table I. Electrocardiogram showed prolonged QT interval (Fig. 1). A gastro-esophageal endoscopy showed mild antral gastritis. Duodenal biopsy demonstrated mild chronic nonspecific inflammation. Urinary excretion of sodium, potassium, phosphorus and magnesium were normal and urinary excretion of calcium was low, therefore

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electrolyte tubular dysfunction was discarded. She denied diarrhoea, vomiting, excessive sweating, alcoholism, use of diuretics, and family history of hypomagnesaemia.

After full investigation, the hypothesis of hypomagnesaemia secondary to PPI was confirmed by exclusion. Omeprazole was replaced by ranitidine 300 mg daily and supplementation of magnesium was started, initially intravenously as magnesium sulfate, and then orally as magnesium carbonate 500mg three times a day. Oral calcium carbonate (1250 mg twice/day) and colecalciferol (1000 UI/day) were also supplemented. Serum levels of magnesium (1.69 mg/dL), total calcium (10.60 mg/dL) and ionised calcium (5.42 mg/dL) improved. However, as she complained of dyspeptic symptoms with ranitidine, it had to be replaced by omeprazole at a lower dose than previously used (20 mg daily).

Despite continuous oral magnesium supplementation, after one month there was a recurrence in the low serum magnesium levels (0.8 mg/dL), which was attributed to the use of omeprazole. After a new suspension of PPI, reintroduction of ranitidine and optimisation of antireflux environmental measures, magnesium serum levels returned to normal (1.69 mg/dL), as shown in Fig. 2.

Discussion

Although magnesium has been considered a “forgotten ion” (7), hypomagnesaemia can be symptomatic and cause non-specific (asthenia and paresthesias) and life-threatening manifestations (seizures, severe arrhythmias and cardiac arrest) (6, 9-11). Hypocalcaemia can also occur in association with hypomagnesaemia (6, 7, 9, 10, 12). Possible causes of hypomagnesaemia can be divided in insufficient intake, inappropriate gastrointestinal absorption, increased renal loss and redistribution into tissues (6, 9, 10).

Gastrointestinal conditions associated with impaired magnesium absorption are diarrhoea, steatorrhoea and malabsorption syndromes, particularly coeliac disease and short bowel syndrome. Increased renal magnesium loss can be caused by increased flow due to poly-

Table I. Laboratory and complementary exams.

| Exam | Result (normal range) |
|--|-----------------------------------|
| Total serum calcium | 7.1 mg/dL (8.6-10.2) |
| Ionised serum calcium | 3.6 mg/dL (4.6-5.3) |
| Serum magnesium | 0.81 mg/dL (1.58-2.55) |
| Serum phosphorus | 3.8 mg/dL (2.7-4.5) |
| 25-hydroxyvitamin D | 27 ng/mL (30-100) |
| Parathyroid hormone | 55 pg/mL (15-65) |
| 24h-hour urine calcium | 2.31 mg/vol24h (100-320) |
| 24-hour urine magnesium, phosphorus, sodium, potassium | Normal |
| Bone densitometry | Osteopenia |
| Endoscopy | Mild antral gastritis |
| Duodenal biopsy | Chronic non-specific inflammation |
| AEA and ATA | Negative |

AEA: anti-endomisium antibody; ATA: anti-transglutaminase antibody

Fig. 1. Elettrocardiogram. Prolonged QT interval.

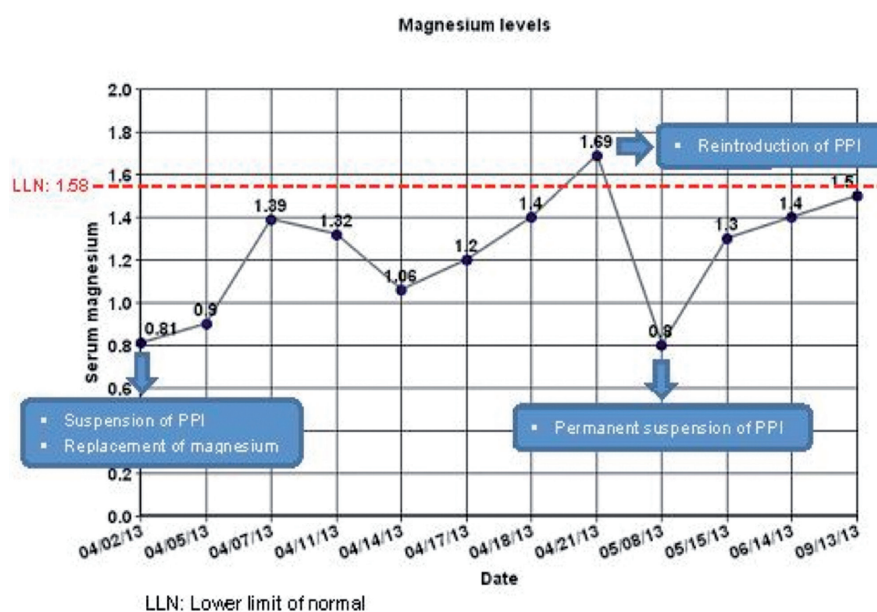
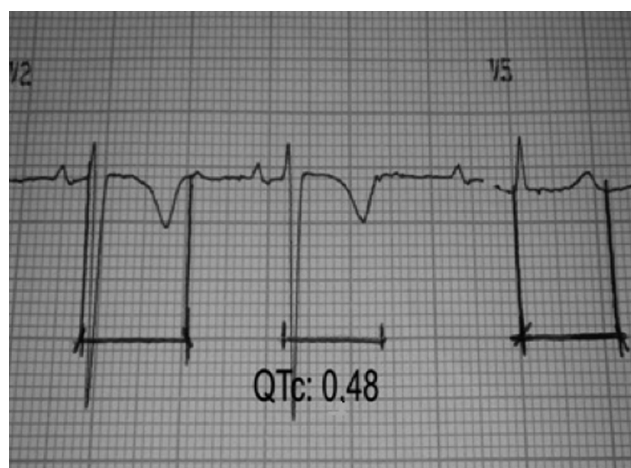


Fig. 2. Serum magnesium levels (mg/dL).

uria or by decreased tubular reabsorption (6, 7).

Conditions associated with decreased renal magnesium reabsorption are use of some drugs (like loop and thiazide diuretics, aminoglycosides, amphotericin B and calcineurin inhibitors), primary aldosteronism, hypercalcaemia and genetic syndromes (6, 7).

Despite the well-established security and worldwide prescription, the U.S. Food and Drug Administration (FDA) warned recently about drug-induced hypomagnesaemia caused by PPIs (13). The main possible mechanism by which PPIs may lead to hypomagnesaemia seems to be gastrointestinal magnesium loss. PPIs may affect the active transport pathway of magnesium through Transient Receptor Potential Melastatin 6 (TRPM6), a transcellular magnesium transporter present, specially, at intestinal mucosa and renal tubule. Alternatively, susceptibility to reduced intestinal magnesium absorption could be attributed to TRPM6 mutations, that is often accompanied by secondary hypocalcaemia (6, 7). Experimental models have been used to better study possible polymorphisms for TRPM6 gene that might clarify increased susceptibility to this condition (9).

Hypomagnesaemia secondary to the use of PPIs is a diagnosis of exclusion and the other hypotheses should be investigated, as in the present case. The patient had no previous history of hypomagnesaemia associated conditions, and tubular dysfunction and malabsorption syndromes were excluded as well. Risk factors for PPI associated hypomagnesaemia are old age, chronic

use of PPIs and concomitant use of other drugs associated with hypomagnesaemia (7) and risk is not related to PPI dose or specific drug (13, 14).

In general, magnesium supplementation is not sufficient to correct hypomagnesaemia and PPI must be discontinued (15). In our patient, the reintroduction of PPI due to worsening of dyspeptic symptoms led to recurrence of hypomagnesaemia, supporting a possible relation with PPI use.

According to the recent observations of side effects related to the long-term use of PPI, these patients should have their magnesium and calcium serum levels checked periodically (4, 12, 15). Non-specific symptoms such as asthenia and generalised paresthesia should not be neglected.

In SSc, as chronic GER can cause oesophagus adenocarcinoma (1) and contribute to interstitial lung disease (2), long-term use of PPI should not be withdrawn in those who really need it, but the PPIs dose should be adjusted to the lowest effective dose and only for as long as clinically needed.

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