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Thiazide and proton pump inhibitor-induced severe hypomagnesemia and hypocalcemia: case report

Hipomagnesemia e hipocalcemia graves induzidas pelo uso concomitante de inibidor de bomba de prótons e tiazídico: relato de caso

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ABSTRACT: *Introduction*: Proton pump inhibitors (PPIs) and thiazide diuretics are medications frequently used in primary care. *Objective*: to report a case of a patient with thiazide and proton pump inhibitor-induced severe hypomagnesemia and hypocalcemia and to review its etiology and pathophysiology, besides the measures that can be carried out to reduce the risk of these abnormalities. *Case presentation*: A 69-year-old man came to the clinic due to involuntary muscle contractions and progressive walking difficulties for 3 months. He had been taking omeprazole 20 mg / day for 20 years and hydrochlorothiazide 25 mg/ day for 2 years. On physical examination, he showed signs of neuromuscular hyperexcitability (fasciculations, muscle spasms, positive Chvostek and Trousseau sign). Laboratory tests indicated severe hypomagnesaemia and hypocalcemia, with parathormone concentrations inappropriately within the normal range. The patient was hospitalized and, with magnesium and calcium replacement and medication discontinuation, presented permanent resolution of the condition. Conclusion: Severe hypomagnesemia may be a complication of long-term administration of proton pump inhibitors (PPIs) and thiazide diuretics. PPIs cause a reduction in the active magnesium intestinal absorption pathway, while thiazides increase renal magnesium excretion. Severe hypomagnesaemia often leads to hypocalcemia by inducing a reduction in the secretion and action of parathyroid hormone. To avoid this potentially serious side effect, we recommend some precautions to be followed when a patient must be treated with a gastric acid suppressant and a thiazide.

Keywords: Magnesium deficiency; Hypocalcemia; Hypoparathyroidism; Omeprazole; Diuretics; Proton pump inhibitors.

RESUMO: *Introdução:* Inibidores de bomba de prótons (IBP) e diuréticos tiazídicos são medicações frequentemente empregadas na atenção primária. Objetivo: relatar o caso de um paciente com hipocalcemia e hipomagnesemia graves induzidas pela associação de omeprazol e hidroclorotiazida, discutindo a etiologia e fisiopatologia do quadro, além de medidas clínicas que podem ser adotadas para mitigar o risco do surgimento dessas complicações. *Apresentação do caso:* Homem de 69 anos procurou ambulatório por queixas de contrações musculares involuntárias e dificuldade progressiva de marcha há 3 meses. Vinha fazendo uso de omeprazol 20 mg/dia há 20 anos e hidroclorotiazida 25 mg/dia há 2 anos. No exame físico, apresentava sinais de hiperexcitabilidade neuromuscular (fasciculações, espasmos musculares, sinal de Chvostek e Trousseau positivos). Exames laboratoriais indicaram hipomagnesemia e hipocalcemia graves, com concentrações de paratormônio inapropriadamente dentro da faixa da normalidade. O paciente foi hospitalizado e, com reposição de magnésio e cálcio e suspensão das medicações, apresentou resolução permanente do quadro. *Conclusão:* Hipomagnesemia grave é uma possível complicação do uso a longo prazo de IBPs, principalmente quando associado a diuréticos tiazídicos. IBPs causam uma redução na via de absorção ativa do magnésio pelo intestino, enquanto tiazídicos aumentam a excreção renal de magnésio. A hipomagnesemia grave frequentemente leva à hipocalcemia por induzir uma redução na secreção e na ação do paratormônio. A fim de evitar esse efeito colateral potencialmente grave, propomos diversas medidas a serem adotadas em pacientes com indicação de serem tratados com supressores de acidez gástrica e tiazídicos.

Palavras-chave: Deficiência de magnésio; Hipocalcemia; Hipoparatireoidismo; Omeprazol; Diuréticos; Inibidores da bomba de prótons.

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INTRODUCTION

Proton pump inhibitors (PPI) and thiazide diuretics are often employed to treat dyspepsia and arterial hypertension, respectively[1,2]. This report aims to describe the potentially serious clinical picture of a patient with severe hypocalcemia resulting from hypomagnesemia due to the chronic use of a PPI (omeprazole) and a thiazide (hydrochlorothiazide). Recommendations regarding the association of these drugs are also discussed. Hypomagnesemia is an electrolyte disorder that is still poorly studied and rarely investigated in clinical practice[3]. However, hypomagnesemia may be life risk, especially when it is severe[4].

The medical record of one patient was reviewed to prepare the case report. The study was approved by the Ethical Board of Universidade Anhembi Morumbi.

CASE REPORT

A 69-years-old male patient sought outpatient medical care in May 2019 due to progressive fatigue for 6 months. Moreover, in the last 3 months, he had involuntary muscle contractions, muscle stiffness, paresthesia, dizziness, memory impairment and gait difficulty, which led to difficulties in usual tasks, such as taking a shower. Personal history: dyspepsia, arterial hypertension for 20 years and chronic obstructive pulmonary disease (pulmonary emphysema). Habits: smoker of 20 cigarettes/day for 50 years; no alcoholic beverage consumption. He was under treatment with losartana 50 mg/day, hydrochlorothiazide 25 mg/day (in the last 2 years ago) and omeprazole 20 mg/day (in the last 20 years ago). In physical examination, he was afebrile, temporally and spatially disoriented, hydrated, slightly tachypneic and had body mass index of 22.5 kg/m^2, blood pressure of 120x80 mmHg and a regular heart rate of 88 bpm. He also had muscle fasciculations and intense muscle spasms at the slightest touch of limbs or face. Chvostek and Trousseau signs were also present. He had a hyperinflated chest, slightly reduced breath sounds and mild expiratory wheezing, with no other changes in the remainder of the exam. The patient was referred to the emergency care unit, where laboratory tests revealed hypomagnesemia and hypocalcemia. He was then hospitalized on May 23, 2019. Table 1 shows the results of laboratory tests on admission, during hospitalization and 14 months after hospital discharge. During hospitalization, IBP and thiazide were discontinued, calcium and magnesium were replaced and inhaled beta-2 agonists and glucocorticoids were initiated. Electrolyte levels were all restored to normal and there was improvement in dyspnea and permanent remission of other symptoms.

On May 27, 2019, with a partial correction of hypomagnesemia and hypocalcemia, there was na increase in parathormone concentrations. This suggested that the severe hypomagnesemia found on hospital admission was preventing the proper secretion of parathormone. Upper digestive endoscopy examination revealed mild enanthematous pangastritis. Abdominal computed tomography (CT) and cervical ultrasound were normal and chest CT showed only signs of chronic obstructive pulmonary disease. A final diagnosis of hypocalcemia and hyperphosphatemia due to dysfunction in the synthesis and action of parathormone, resulting from hypomagnesemia due to the chronic administration of PPI and a thiazide diuretic, was made.

In July 2020, the patient returns to the clinic, without symptoms or signs of neuromuscular abnormalities. He was under treatment with losartana and anlodipine and denied intake of any magnesium or calcium supplementation. Laboratory tests revealed normal serum concentrations of Magnesium (1.8 mg/dL) and total calcium (8.3 mg/dL), as shown in Table 1.

Table 1: Results of laboratory tests performed at hospital admission, during hospitalization and after hospital discharge.

	Hospital admission	**During hospitalization (calcium and magnesium replacement)**		**Outpatient**
Serum concentrations and reference values	May 23, 2019	May 27, 2019	May 30, 2019	July, 2020
Magnesium (1.6-2.6 mg/dL)	0.5	1.5	1.8	1.8
Total calcium (8.2-10.2 mg/dL)	5.2	7.2	8.8	8.3
Ionic calcium (1.17-1.32 mmol/L)	0.6	0.93		
Phosphorus (2.3-4.6 mg/dL)	6.7		3.9	
Parathormone (12-65 pg/mL)	45	192	75	
25 hydroxi-vitamin D (30-60 ng/mL)	42			
Urea (19-49 mg/dL)	59	51	57	
Creatinine (0.6-1.4 mg/dL)	1.7	1.1	1.4	1.6
Sodium (135-145 mmol/L)	143	138		137
Potassium (3.5-5.0 mEq/L)	3.6	3.5		
Glucose (70-99 mg/dL)	90			
Albumin (3.5-5.0 g/dL)	3.3			

DISCUSSION AND LITERATURE REVIEW

Magnesium homeostasis is primarily determined by its intestinal absorption and renal excretion[4]. Hypomagnesemia may result primarily from low oral magnesium intake, reduced intestinal absorption, and increased renal or gastrointestinal magnesium excretion. Therefore, several conditions, such as alcoholism, decompensated diabetes mellitus, pancreatitis and chronic diarrhea can lead to hypomagnesemia[5]. Grains beans, oil seeds spinach and avocados are great sources of magnesium[3].

Hypomagnesemia is defined as a magnesium concentration below 1.6 mg/dL, with or without body magnesium depletion. Significant signs and symptoms are more likely to develop when magnesium concentrations fall below 1.2 mg/dL[3,5].

In the Netherlands, the largest study in the general population carried out so far[6] showed a that 2% of outpatients over 55 years of age had hypomagnesemia and 0.06% had severe hypomagnesemia (below 1.22 mg/dL). Severe hypomagnesemia often leads to hypokalemia and, ultimately, to hypocalcemia[4]. Hypomagnesemia and the electrolyte abnormalities it triggers lead to symptoms of weakness, cramps, neuromuscular hyperexcitability (cramps, tremors, carpopedal spasms, involuntary muscle contractions, fasciculations, tetany and seizures), neuropsychiatric disorders (apathy, delirium and coma) and arrhythmias or electrocardiographic changes such as ST-segment depression, PR interval prolongation or QRS complex widening[3,4]. Asymptomatic hypomagnesemia may also be a risk factor for diabetes mellitus and its complications, arterial hypertension, greater progression of chronic kidney disease, atherosclerosis, osteoporosis, asthma and migraine[3].

Hypoparathyroidism is a condition characterized by hypocalcemia due to inability of parathyroid glands to secrete parathormone and/or inability of parathormone to act on peripheral tissues. The most common cause of hypoparathyroidism is iatrogenic, due to accidental removal or injury of parathyroids or damage to their arterial irrigation during thyroidectomies[7]. Hypomagnesemia can lead to hypocalcemia due to functional hypoparathyroidism caused by reduced PTH secretion and tissue resistance to its action[7,8,9]. Therefore, serum magnesium measurement should be evaluated in all patients with hypocalcemia, to exclude hypomagnesemia as an etiology[7].

The PTH receptor that mediates its effects on bones and kidneys is the type 1 parathyroid Hormone receptor (PTH1R). This receptor, when activated, leads to the activation of the stimulatory G protein, which, in turn, activates adenylate cyclase, a key enzyme to of cyclic AMP, a second messenger. Magnesium is a cofactor of adenylate cyclase in the kidneys and, therefore, its deficiency leads to resistance to the action of PTH in the kidney[9]. On admission to hospital (table 1), even with a PTH concentration within the reference value, there was severe hypocalcemia, which is compatible with a resistance to the action of PTH resulting from hypomagnesemia. Previous studies have also shown that magnesium is of great importance in PTH secretion, although its exact mechanism of action on endocrine parathyroid cells is still unknown[7,8,9]. In patients with hypomagnesemia, PTH secretion increases within a few minutes after magnesium infusion[8]. On admission to hospital (table 1), the patient had a serum PTH concentrations of 45 pg/mL, inappropriately within the reference value, despite the severe hypocalcemia (5.2 mg/dL). As soon as magnesium was replaced, magnesemia increased from 0.5 mg/dL to 1.5 mg/dL. An increase in serum PTH concentrations to 192 pg/mL was then observed, despite a less pronounced hypocalcemia of 7.2 mg/dL (may 27th, 2019). This laboratory response is compatible with a deficiency in PTH secretion induced by severe hypomagnesemia on hospital admission, which was reversed with magnesium replacement.

Classically, hypocalcemia leads to paresthesia on the face or distal limbs, weakness, myalgia and increased neuromuscular excitability[7]. On physical examination, the main signs of hypocalcemia are related to neuromuscular excitability. Trousseau's sign is characterized by involuntary contraction of forearm muscle with flexion of the wrist and metacarpophalangeal joints and adduction of the thumb (carpopedal spasm or "obstetrician's hands"), during a cuff inflation with blood pressure 10 to 20 mmHg above systolic blood pressure for 3 minutes. This sign is very specific to hypocalcemia, buy it is found in 4% of normal individuals. Chvostek's sign is characterized by homolateral contraction of the muscles around the lips and other facial muscle when the facial nerve is tapped along its path anterior to ear pinna. This sign is found in 10% of normal individuals and, therefore, is less specific for hypocalcemia[7].

Thiazide diuretics may lead to hypomagnesemia[6,9,12]. Thiazides reduce the expression of magnesium channels in the epithelium of the distal renal tubules, witch are called TRPM6 (Transient Receptor Potential Cation Channel Subfamily M Member 6), increasing renal magnesium excretion[10,13]. Thiazides, however, are able to decrease calciuria and may reduce the severity of hypocalcemia induced by hypoparathyroidism triggered by hypomagnesemia[10,14]. In most patients who use thiazides alone, hypomagnesemia is not a frequent abnormality and serum magnesium monitoring is not recommended[10]. However, when a proton pump inhibitor (PPIs) is associated to a thiazide, greater caution is needed. Uehara et al.[14] identified a 42% increase in the prevalence of hypomagnesemia in users of thiazides concomitantly with PPIs, when compared to the isolated use of thiazides. Intestinal magnesium absorption depends on a passive and an active transport mechanism[4]. The active transport mechanism is reduced in PPI users, as it triggers a lower

expression of magnesium transporting channels in the apical membrane of the intestinal epithelium, called the melastine-6/7 transient receptor potential cation channel (TRPM6/7)[4].

Most studies indicate that the use of PPIs is associated with a higher risk of hypomagnesemia[4,5,11,12,15,16]. In outpatients, the use of PPIs led to a 1.66[12] to 2-fold[16] greater risk of hypomagnesemia and 1.79 greater[12] risk of severe hypomagnesemia. The time to development of hypomagnesemia with the use of PPIs is quite variable, from days to more than 10 years[17], but generally greater than 6 months[4,16]. Since passive transport mechanism is not disturbed, hypomagnesemia can be partially or completely corrected by oral supplementation of high doses of magnesium[4]. The discontinuation of PPIs leads to a rapid improvement in hypomagnesemia in those patients, often within a week[5,11]. Although it is controversial that type 2 histamine receptor antagonists (ranitidine, famotidine and cimetidine) may increase the risk of mild forms of hypomagnesemia[11,12,16], they have not been related to the development of severe forms of hypomagnesemia[11,12].

The risk factors for hypomagnesemia in patients using PPIs are: age above 50 years old (with even greater risk above 65 years old), duration of treatment with PPIs of 6 months or more, presence of other factor that predispose to hypomagnesemia (such as alcoholism, diabetes mellitus and concomitant use of thiazides or loop diuretics) and concomitant renal dysfunction[11,16,18]. In a study with FDA data, the risk of hypomagnesemia varied between different PPIs, with pantoprazole and omeprazole achieving the highest risk[18].

In this case report, a patient over 65 years old with chronic renal insufficiency had been using omeprazole for 20 years ad thiazide diuretic for 2 years, all of which are risk factors for severe hypomagnesemia related to the use of PPIs. Hypokalemia was not verified and, possibly, the use of losartan, an angiotensin II receptor blocker, has contributed to the maintenance of potassium in the lower reference range.

CONCLUSIONS

Surveillance of symptoms and signs of severe hypocalcemia in patients using PPIs and thiazides is needed[11]. PPIs shall be prescribed only in situations where there is a clear indication and for the shortest time possible[2] and thiazides should be prescribed in low doses[1]. Since type 2 histamine receptor antagonists do not lead to an increased risk of severe hypomagnesemia, replacing PPIs with this drug may be useful in chronic PPI users[11]. However, with the recent restriction on the marketing of ranitidine in Brazil, a greater number of patients may start using PPIs, leading to a higher prevalence of severe forms of hypomagnesemia. The intake of magnesium-rich foods or prescription of magnesium supplements may be encouraged in patients at higher risk of hypomagnesemia.

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