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Case Report

Calcium-alkali syndrome: A rare cause of hypercalcemia?

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Abstract

Severe hypercalcemia is an electrolyte disorder with variable clinical expression that can be serious if appropriate corrective measures are not taken. Among the main causes of hypercalcemia are primary hyperparathyroidism and neoplasms. However, it appears that cases of a third cause of secondary hypercalcemia are increasing. The calcium and alkali syndrome, formerly known as milk-alkali syndrome, is a disorder resulting from excessive intake of calcium and alkaline compounds, leading to hypercalcemia, metabolic alkalosis, and renal failure. One of the contributors to this syndrome is the ingestion of calcium carbonate antacids for dyspepsia, which are also used (sometimes along with vitamin D metabolites) to treat bone pathologies or in post-surgical medical treatments following thyroid and parathyroid gland interventions.

We describe four cases of patients who developed this syndrome with severe hipercalcemia in the context of post-surgical hypoparathyroidism treatment, aiming to raise awareness among clinicians and patients about the potential risks of calcium supplements associated with calcitriol.

Keywords:
Hypercalcemia. Alkalosis. Calcium. Carbonate. Calcitriol.

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INTRODUCTION

Hypercalcemia is a relatively common finding in the routine clinical practice. It results from failed renal calcium excretion to compensate for the increased entry of calcium into the circulation (1). Primary hyperparathyroidism and hypercalcemia due to a malignant neoplastic process are among the main causes, although multiple situations can cause elevated serum calcium levels, albeit less frequently (2). Correctly identifying the cause of elevated calcium levels is crucial for applying the appropriate treatment (3).

Calcitriol treatments are indicated for patients with renal osteodystrophy, idiopathic postoperative hypoparathyroidism (4), pseudohypoparathyroidism, vitamin D-dependent rickets (5) or resistant rickets, osteomalacia, and for preoperative treatment in primary hyperparathyroidism. Calcium carbonate is indicated to prevent calcium deficiency and as an adjunct in the management of osteoporosis (6). Both drugs have hypercalcemia as a very common adverse reaction (more than 1 case per 10 patients treated) for calcitriol and less common (more than 1 case per 1000 patients treated) for calcium carbonate.

The calcium-alkali syndrome (CAS) is the most updated term for the widely known milk-alkali syndrome. This condition is characterized by the triad of hypercalcemia, metabolic alkalosis, and varying degrees of renal failure due to calcium ingestion along with an absorbable alkali (7,8).

The following reports 4 cases of CAS that presented with severe hypercalcemia to raise awareness among clinicians and patients on the potential dangers of calcitriol-associated calcium supplements.

CASE REPORTS

CASE REPORT #1

A 77-year-old woman with a history of dyslipidemia and chronic ischemic heart disease, with preserved renal function (serum creatinine levels of 1.15 mg/dL) on enalapril, torasemide, and acetylsalicylic acid. She was diagnosed with primary hyperparathyroidism, for which a right parathyroidectomy was performed. Due to persistent symptoms, another surgery involving left parathyroidectomy and hemithyroidectomy was required. Pharmacological treatment with calcium carbonate (2 g every 24 hours) and calcitriol (0.5 µg every 24 hours) was initiated. Despite treatment, the patient exhibited hypocalcemia with hyperreflexia and a positive Trousseau sign, requiring hospitalization for electrolyte replenishment. The electrocardiogram performed at admission was normal. After discharge, the calcium carbonate dose was increased up to 5 g every 6 hours. In a routine check-up, the patient had calcium levels of 17.1 mg/dL (8.7-10.4 mg/dL) with ionic calcium levels of 2.3 mmol/L (1-1.4 mmol/L), creatinine levels of 1.93 mg/dL (0.5-1.1 mg/dL), bicarbonate levels of 33 mmol/L (22-28 mmol/L), and phosphate levels of 2.2 mg/dL (2.4-5.1 mg/dL), suppressed PTH (15-65 pg/mL), and 25-hydroxyvitamin D (25OHD) of 21.1 ng/mL (30-40 ng/mL). In light of these findings, the attending physician was contacted to expand the lab tests, obtaining a pH value of 7.43 (7.32-7.42).

The patient was called to the hospital, and treatment with calcium carbonate and calcitriol was immediately discontinued. Upon examination, the patient was asymptomatic, with no electrocardiographic signs suggestive of complications from hypercalcemia, so no other corrective measures were applied. In subsequent controls, after the withdrawal of calcitriol and calcium carbonate, the patient showed a progressively improved renal function and a decrease in calcium levels to reference values.

CASE REPORT #2

A 51-year-old man without relevant clinical history or notable analytical changes in previous controls, with recent creatinine levels of 1.14 mg/dL, required total thyroidectomy for retrosternal goiter. After a second surgery due to persistent symptoms, pharmacological treatment with levothyroxine (125 µg every 24 h), calcium carbonate (4.5 g every 24 h), and calcitriol (0.50 µg every 24 hours) was initiated. In a routine check-up, the patient had calcium levels of 13.1 mg/dL with ionic calcium levels of 1.57 mmol/L, creatinine levels of 2.23 mg/dL, a pH of 7.39, bicarbonate levels of 31.1 mmol/L, suppressed PTH, and 25OHD of 27 ng/mL.

The patient was called to the hospital, where the lab test results were confirmed. Upon examination, he presented with back pain, paresthesia, asthenia, and generalized muscle pain that had increased in recent days. The pharmacological treatment was immediately discontinued, and the patient was hospitalized for fluid therapy (300 mL of 0.9% NaCl every 24 h) to hydrate and minimize renal damage, and zoledronic acid was used as an inhibitor of bone resorption to prevent the release of calcium from the bone (a 15-minute 4 mg/5 mL ampoule infusion)9. When calcium levels went back to normal (8.2 mg/dL), the patient was discharged after 4 days of hospitalization. An interconsultation with the Nephrology Unit was conducted due to persistent renal failure, with creatinine values of 1.63 mg/dL. A renal ultrasound detected radiopaque calculi suggestive of calcium oxalate in both kidneys. After getting rid of the stones, the patient showed complete recovery of renal function.

CASE REPORT #3

A 58-year-old woman diagnosed with primary hyperparathyroidism underwent a left parathyroidectomy. Due to the progression of osteoporosis and persistent symptoms, total parathyroidectomy was performed. She was prescribed calcium carbonate (3 g every 24 hours), calcitriol (1 µg every 24 hours), levothyroxine (50 µg every 24 hours), and esomeprazole (40 mg every 24 hours) after surgery. Pre-episode analyses did not show any significant findings. The most recent creatinine determination before the episode was 1.37 mg/dL.

The patient presented to the ER with a several day-history of general malaise, constipation, and reduced urine output, along with nausea, vomiting, and generalized weakness. Lab test results showed creatinine levels of 2.73 mg/dL, calcium levels of 17.3 mg/dL with ionic calcium levels of 2.08 mmol/L, suppressed PTH, pH of 7.40, bicarbonate levels of 33.1 mmol/L, and TSH levels of 1.05 µg/mL (0.27-5.0 µg/mL).

Given these results, the patient was admitted with a diagnosis of renal failure and hypercalcemia. IV fluid therapy (300 mL of 0.9% NaCl every 24 h) was administered to preserve renal function and reduce calcium levels, along with methylprednisolone (40 mg every 12 hours in intermittent dilution) followed by the immediate withdrawal of calcium carbonate and calcitriol. Three days after admission, calcium levels went back to normal (9.8 mg/dL), and creatinine improved slightly (2.17 mg/dL). The patient was discharged, with follow-up in Primary Care.

CASE REPORT #4

A 63-year-old woman with dyslipidemia and depression treated with atorvastatin and fluoxetine had undergone a total thyroidectomy years earlier treated for postoperative hypothyroidism with levothyroxine (100 µg every 24 hours), calcium carbonate (2 g every 12 hours), and calcitriol (0.5 µg every 12 hours). She was admitted to the ER with symptoms of dizziness, weakness, and vomiting, along with a blood pressure of 164/90 mmHg upon initial examination. Previous tests showed no significant changes, and renal function and calcium levels were within the normal range a few months earlier during a routine analysis (creatinine levels of 0.9 mg/dL and total calcium levels of 10.4 mg/dL).

Lab test results showed total calcium levels of 19 mg/dL, ionic calcium levels of 2.08 mmol/L, bicarbonate levels of 31.8 mmol/L, a pH of 7.45, suppressed PTH, and creatinine levels of 1.31 mg/dL, indicating a diagnosis of severe secondary hypercalcemia. Treatment with fluids, methylprednisolone (40 mg every 24 hours in intermittent dilution), and IV zoledronic acid (4 mg/100 mL over 15 minutes) was initiated.

The patient was hospitalized, and calcium carbonate and calcitriol were immediately discontinued. Calcium levels were monitored, reaching values of up to 11.4 mg/dL and a pH of 7.52 after 2 days of hospitalization. The patient remained hospitalized, and on the 4th day, calcium levels were 10.0 mg/dL and pH, 7.42. At discharge, follow-up tests were scheduled 2 months later, and therapy with calcium carbonate and calcitriol was reinstated at reduced doses (500 mg every 12 hours and 0.5 µg per day, respectively).

DISCUSSION

Since the introduction of proton pump inhibitors for the management of dyspepsia, CAS has been considered a rare cause of hypercalcemia (< 1% of cases) (10). However, numerous authors suggest that the incidence of this syndrome is increasing. In recent series studied, it is responsible for more than 12% of hypercalcemia cases. These data position CAS as the third leading cause of hypercalcemia (7) and the second leading cause of severe hypercalcemia (7,8). This situation can be explained by the increased prescription of calcium supplements considered safe for various conditions, such as hypoparathyroidism, or physiological processes like menopause (8-11). However, the cases we present highlight that these drugs can lead to severe hypercalcemia when consumed over prolonged periods.

All our patients had previously undergone surgery, resulting in a status of postoperative hypoparathyroidism with suppressed PTH levels. They were on calcium carbonate, which, in addition to providing calcium that contributes to hypercalcemia, incorporates the alkaline component which is essential for the development of the syndrome. This is because the components of calcium carbonate contribute to the increase of plasma bicarbonate, which decreases its renal excretion (12). None of the patients were previously on ant other treatments that could cause hypercalcemia, such as thiazide diuretics, so the only plausible iatrogenic cause is due to calcitriol and calcium carbonate. Metabolic alkalosis would also increase calcium reabsorption at tubular level. Additionally, the fact that they were on supplements of vitamin D metabolites (calcitriol) with effects on bone resorption, absorption, and reabsorption of calcium at intestinal and renal levels, respectively, and PTH secretion (13), caused a synergistic hypercalcemic effect, contributing to the overall clinical picture (14,15). The technical sheet for calcitriol recommends monitoring calcium levels, at least, twice a week when initiating treatment and, once the optimal dose is adjusted, calcium levels should be checked monthly.

The emergency treatment of CAS-induced hypercalcemia involves the withdrawal of calcium carbonate and calcitriol, and if necessary, fluid therapy,

zoledronic acid, and methylprednisolone, the latter used in specific situations as the first-line therapy for calcitriol-induced hypercalcemia.

Although the pathophysiological mechanism of CAS is not yet clearly elucidated, we can say that the trigger is hypercalcemia due to the imbalance between increased intestinal calcium absorption and the excretion capacity of the kidney (12). This hypercalcemia indirectly increases the reabsorption of bicarbonate in the kidney, causing alkalosis.

CAS is becoming an important public health issue due to the growing number of reported cases. Therefore, clinicians should consider this entity, especially in patients receiving continuous calcium supplements and a vitamin D metabolite, as they are at higher risk. Additionally, it is advisable to maintain close monitoring of renal function and pH in this group to enable early diagnosis and prevent possible complications.

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