CASE REPORT

Milk-Alkali Syndrome: A Century Old Cause of Resurgence of Severe Hypercalcemia Due to Excessive Use of Calcium Supplements

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ABSTRACT

The milk-alkali syndrome (MAS) is characterized by a triad of elevated calcium levels, metabolic alkalosis and acute kidney injury that commonly occurs due to the combined intake of large amounts of calcium and absorbable alkali. The syndrome can have an acute onset with the rapid development of hypercalcemia and, if left untreated, may result in acute renal failure and metastatic calcification. An increased number of cases of MAS have recently been reported. This is likely due to the common use of over the counter (OTC) preparations of calcium for preventing and treating osteoporosis in postmenopausal women. Herein, we report a case of severe hypercalcemia due to prolonged intake of calcium carbonate supplements in the absence of any alkali.

Keywords: Hypercalcemia, renal failure, alkalosis, calcium supplements

The milk-alkali syndrome (MAS) consists of the triad of hypercalcemia, metabolic alkalosis and varying degrees of renal failure associated with the ingestion of large amounts of calcium and absorbable alkali. This syndrome was discovered in the 1930s after treatment of peptic ulcer disease with milk and sodium bicarbonate had become common.[1] Once a classic cause of hypercalcemia, the MAS virtually disappeared with the advent of new therapies of peptic ulcer disease and, by 1985, was considered the cause of <1% of cases of hypercalcemia.[2]

Recently, however, an increased number of cases of MAS have been reported. This is likely due to the common use of over the counter (OTC) calcium preparations for preventing and treating osteoporosis in postmenopausal women. Calcium carbonate is also frequently prescribed to patients with chronic kidney disease to prevent secondary hyperparathyroidism. Various scholars have also suggested changing the syndrome's name to calcium-alkali syndrome due to the changing etiopathology.[3] MAS now accounts for more than 10% of the cases of hypercalcemia and is believed to be the third most common cause of in-hospital hypercalcemia, after hyperparathyroidism and malignant neoplasms.[4]

CASE REPORT

A 71-year-old normotensive, nondiabetic, euthyroid female, presented with confusion, irrelevant talks and urinary incontinence. Her blood pressure (BP) was 160/84 mmHg and random blood sugar (RBS) was 127 mg/dL. Routine blood investigations revealed, hemoglobin - 13.2 g/dL, urea - 103 mg/dL, creatinine - 4.2 mg/dL, total calcium - 14.9 mg/dL, phosphorous - 4.2 mg/dL, albumin - 3.9 g/dL, her arterial blood gas (ABG) showed metabolic alkalosis, with pH of 7.54. She gave history of taking analgesics for joint pains, and supplements of calcium carbonate for osteoporosis for last 20 years.

She was treated with saline diuresis and calcitonin for 2 days, and her symptoms and renal functions started improving. Other investigations revealed thyroid-stimulating hormone (TSH) of 6.2 mIU/mL, 25(OH)-vitamin-D of 40.4 ng/mL and normal serum protein electrophoresis. Despite high serum calcium levels, her parathyroid hormone (PTH) was not suppressed and intact PTH was found to be 46.1 pg/mL. But the ^{99m}TcSestaMIBI scan did not localize any parathyroid adenoma and positron emission tomography-computed tomography (PET-CT) ruled out possibility of any paraneoplastic syndrome.

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On the basis of metabolic alkalosis even in the setting of severe renal dysfunction, and excluding other causes of hypercalcemia, a diagnosis of MAS was made. On further questioning, the patient admitted to perhaps taking more calcium than she should have. But there was no history of any antacid intake. Within a week after admission, her renal functions improved significantly, her blood urea reduced to 50 mg/dL, creatinine to 1.8 mg/dL and total calcium came down to 8.5 mg/dL. The patient was discharged with clear instructions to avoid any calcium carbonate supplements.

DISCUSSION

Despite extensive clinical experience, scant data are available on the pathogenesis of MAS. Throughout the years, several contributing factors have been proposed, including loss of gastric juice, pre-existing renal disease, insufficient chloride intake, hemorrhage, anemia and impaired liver function. Ingestion of excessive quantities of calcium and absorbable alkali is a prerequisite for establishing the diagnosis. What constitutes "excessive" is unclear but generally indicates at least 4 to 5 g of calcium carbonate daily.[5]

For hypercalcemia to develop, calcium intake must be excessive, but inability to excrete the excess calcium is also an essential part of the process. Because the skeletal system does not have unlimited calcium buffer capacity, tight regulation of calcium absorption from the small intestine and excretion by the kidneys are paramount to maintain serum calcium levels. Individual variations in the buffering capacity of bone may also have a role in the susceptibility to development of hypercalcemia.

Increased intake of calcium results in decreased 25-hydroxylation of vitamin D by the kidneys, which leads to a marked decrease of fractional calcium absorption in the small intestine. In certain individuals, high urinary calcium excretion indicative of high intestinal absorption persists despite continuous calcium ingestion and suppressed 1,25-(OH) vitamin D levels. Under normal conditions, renal calcium excretion is a close reflection of calcium absorption. However, if large quantities of calcium are continuously ingested and the renal excretory capacity is blocked, hypercalcemia may be a predictable result. Failure to fully suppress calcitriol levels may contribute to development of MAS in a subset of individuals with high oral calcium intake.[6]

The PTH level should be suppressed by the high serum calcium level in patients with MAS. But in the setting of severe renal dysfunction, PTH level is raised. Renal dysfunction is also associated with metabolic acidosis. But in the setting of MAS, metabolic alkalosis is the essential feature. Differentiating MAS from other causes of hypercalcemia is important as treatment is supportive. Adequate hydration to correct hypovolemia, along with loop diuretics, like furosemide, to increase urinary calcium excretion may be sufficient to correct hypercalcemia. Bisphosphonates should generally be avoided in patients with MAS as they can cause prolonged hypocalcemia.[7]

CONCLUSION

The resurgence of MAS in the current era is a result of increased osteoporosis awareness and routine use of calcium carbonate supplements for prevention. The public needs to be educated about calcium supplementation and the potential adverse effects if the recommended dosage is exceeded. Daily elemental calcium intake of no more than 2 g is considered safe.[8] However, even doses lower than 2 g daily may result in MAS if additional predisposing factors are present.

The exact pathogenesis of MAS remains uncertain, but a unique interplay between hypercalcemia and alkalosis in the kidneys seems to lead to a self-reinforcing cycle, resulting in the clinical picture of MAS. Treatment is supportive and involves hydration and withdrawal of the offending agent. Physicians and the public need to be aware of the potential adverse effects of ingesting excessive amounts of calcium carbonate.

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