**Brief Communication**

**Milk alkali syndrome induced by calcitriol and calcium bicarbonate in a patient with hypoparathyroidism**

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**A B S T R A C T**

The milk-alkali syndrome (MAS) was a common cause of hypercalcemia, metabolic alkalosis, and renal failure in the early 20th century. This syndrome was first recognized secondary to treatment of peptic ulcer disease with milk and absorbable alkali. Its incidence fell after the introduction of H2-blocker and proton pump inhibitor. Persistent ingestion of calcium carbonate and vitamin D caused MAS. We report a patient presenting with a triad of hypercalcemia, metabolic alkalosis and renal failure secondary to treatment of idiopathic hypoparathyroidism.

**Key words:** Acute kidney injury, hypercalcemia, metabolic alkalosis

**INTRODUCTION**

Most common reason of hypercalcemia is hyperparathyroidism or malignancy. Milk-alkali syndrome (MAS) is a case characterized with hypercalcemia, acute kidney failure, metabolic alkalosis and it is one of the rare reasons of hypercalcemia. This syndrome is classically described after overdose using anti-acides. However, this syndrome had been decreasing with the development of modern ulcer treatment. Because of the usage of calcium containing drugs for the treatment and prevention of osteoporosis and renal osteodystrophy, the incidence of the syndrome started to increase nowadays.

We report a patient presenting with a triad of hypercalcemia, metabolic alkalosis and renal failure secondary to treatment of idiopathic hypoparathyroidism.

**CASE REPORT**

A 56-year-old male patient was consulted in our polyclinic with a 1 week history of fatigue and general weakness. In medical history, he had been taking calcium carbonate (3.0 g/daily) and calcitriol (1 μg/daily) for idiopathic hypoparathyroidism for 5 years. In his physical examination, pulse rate was 70/min and blood pressure was 130/75 mmHg. Patient's general physical status was well and pathological finding was not found on physical exam. Urinalysis was normal. The pertinent laboratory tests revealed severe hypercalcemia, acute kidney injury and metabolic alkalosis [Table 1]. Calcium carbonate and vitamin D treatment were stopped. Intravenous normal saline was administered. After 3 days, his symptoms such as fatigue and weakness resolved and serum levels of calcium, blood urea nitrogen and creatinine regressed.

**DISCUSSION**

MAS consist of the triad of hypercalcemia, metabolic alkalosis and renal insufficiency associated with ingestion of the large amount of calcium and absorbable alkali. Our patient had MAS consisting of hypercalcemia, metabolic alkalosis and acute renal failure due to 3 g/day calcium carbonate and 1 mcg/day calcitriol intake.

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MAS was classically described as secondary to treatment of peptic ulcer disease with Sippy’s regimen, in the modern version of MAS the source of calcium is usually calcium carbonate given for several indications (treatment and prevention of osteoporosis, as a phosphate binder in renal failure and during glucocorticoid therapy).[4]

The pathophysiology of MAS is poorly understood. The risk factors for development of MAS include old age, volume depletion and medication that reduces glomerular filtration rate, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers or non-steroidal anti-inflammatory agents.[5] However, our patient had not been using any drugs except calcium carbonate and oral vitamin D.

Hypercalcemia deteriorates renal functions through dehydration due to polyuria and renal vasoconstriction and resulted in decreased glomerular filtration rate.[4] Metabolic alkalosis secondary to hypercalcemia is caused by increased bicarbonate absorption from proximal tubules.

Hypercalcemia is a life-threatening state. Prognosis is associated with length of progression period, calcium level and underlying reasons.[11] Our patient had characteristics of MAS consisting of hypercalcemia due to intake of calcium carbonate and calcitriol, metabolic alkalosis, acute renal failure, decreased serum parathormone level. As in our case, all symptoms and findings resolve with cessation of calcium intake in acute MAS.

Other possible reasons for hypercalcemia such as malignancies, multiple myeloma, hyperparathyroidism and sarcoidosis must be excluded.[8] Lung radiography, abdominal ultrasound, serum albumine/globuline ratio and hemoglobin values were reported as normal. An endoscopy was not performed for patient who had no symptoms such as nausea and vomiting. Serum potassium level was also normal so pyloric stenosis was not considered.

Excessive taken of vitamin D may cause hypercalcemia by increasing absorption of calcium in the gastrointestinal system. Our patient had been taking 1 mcg/day calcitriol for idiopathic hypoparathyroidism.

MAS have three different forms and they may differ in severity. The acute form is characterized by fatigue, nausea, vomiting, myalgia and irritability. The subacute form may result in band keratopathy and conjunctivitis and in the chronic form is more commonly characterized with nephrocalcinosis and irreversible renal failure may occur.

As for the management, withdrawal of the offending agent and intravenous volume expansion are the most initial steps. Usually, these interventions will reverse hypercalcemia and alkalosis. Renal function can return to normal if the diagnosis of MAS is made early in the course of the disease. Hemodialysis may be required in some clinical settings. In patients presenting with very high serum calcium levels, the addition of furosemide, pamidronate and hydrocortisone may be helpful.[9]

It’s been reported by Tal Alexander et al. that calcitriol associated MAS cases can be treated with pamidronate infusion effectively.[10]

In our case, the calcium carbonate and calcitriol were stopped. Five days later, fatigue and other symptoms improved and his hypercalcemia, metabolic alkalosis and renal function were normalized.

As a result, we wanted to remind that it is important interrogating drug using and a good medical history. Hypercalcemia and metabolic alkalosis can develop rarely even with situations that calcium carbonate and oral calcitriol were used combined.

No matter what the etiology is, in patients who had oral/iv calcium or calcitriol treatments, risk of developing hypercalcemia should be considered and serum calcium levels should be controlled by regular intervals.

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**Table 1: Laboratory data**

|                            | Reference | Baseline | 3 days | 5 days | 10 days |
|---------------------------|-----------|----------|--------|--------|---------|
| Blood urea nitrogen (mg/dl) | 5-20      | 42       | 45     | 23     | 18      |
| Creatinine (mg/dl)        | 0.8-1.2   | 3.6      | 3.47   | 2.21   | 0.9     |
| Calcium (mg/dl)           | 8.4-9.7   | 15       | 13.4   | 9.4    | 8.8     |
| Albumin (g/dl)            | 3.4-4.8   | 3.6      | 3.9    | 3.8    | 3.7     |
| Blood Ph                  | 7.35-7.45 | 7.48     | 7.42   | 7.40   | 7.38    |
| Pco2 (mmHg)               | 38-48     | -        | -      | -      | -       |
| Bicarbonate (mEq/l)       | 21-28     | 31       | 30     | 26     | 24      |
| Potassium (mmol/l)        | 3.5-5.1   | 3.9      | 4.1    | 3.8    | 4.3     |
| Magnesium (mg/dl)         | 1.6-2.6   | 2.38     | 2.1    | 2.01   | 2.3     |
| Phosphate (mg/dl)         | 2.7-4.5   | 2.7      | 3      | 4.9    | 4.3     |
| PTH (pg/ml)               | 12-88     | <0.1     | -      | -      | -       |
| TSH (mIU/l)               | 0.34-0.56 | 2.56     | -      | -      | -       |
| Free T4 (mIU/l)           | 0.61-1.2  | 0.83     | -      | -      | -       |

PTH: Parathyroid hormone, TSH: Thyroid-stimulating hormone
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