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Maryland Poison Center
UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY

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The Maryland Poison Center's Monthly Update: News, Advances, Information

Milk-alkali Syndrome

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In the 1920's, adverse effects including irritability, nausea and vomiting were observed in patients that had been ingesting large amounts of milk, cream and alkali for peptic ulcer disease. These patients also exhibited hypercalcemia, hyperphosphatemia, and elevated serum bicarbonate levels. In 1949, Dr. Charles Burnett termed this constellation of effects as the "milk and alkali syndrome".

Excessive ingestion of calcium-containing supplements and absorbable alkali is the primary cause of milk alkali syndrome (MAS). The development of MAS typically involves an impairment in regulatory mechanisms that allow for the rate of calcium intake to exceed the body's ability to maintain normocalcemia. Increased intestinal absorption, decreased capacity of bone to store calcium, and decreased renal function each contribute to the pathogenesis of MAS. Metabolic alkalosis secondary to alkali ingestion promotes calcium reabsorption from renal tubules, further promoting hypercalcemia. Natriuresis and diuresis through activation of calcium-sensing receptors in the collecting duct and loop of Henle coupled with continual renal dysfunction further maintain a state of hypercalcemia *(Mayo Clin Proc. 2009;84:261-7)*.

Calcium (especially calcium carbonate) and vitamin-D-containing supplements represent common causative agents of modern-day MAS. While MAS typically occurs with repeated, supra-therapeutic ingestions of calcium and alkali-containing substances, there is no specific dose or duration of therapy associated with it. A wide range of calcium carbonate doses from 4-60 grams per day have been reported in cases of MAS *(Clin J Am Soc Nephrol. 2006 Jul;1:641-54).* Patients with pre-existing renal dysfunction or those that are elderly, bulimic, pregnant or post-menopausal have a higher risk of developing MAS.

Symptoms of MAS include headache, muscle weakness, lethargy, nausea, and vomiting. Polydipsia, polyuria, psychosis, and tremor may develop in patients if MAS is left untreated. In more advanced forms of MAS, metastatic calcifications may manifest themselves as band keratopathy or conjunctivitis in the eye, or as nephrocalcinosis in the kidney.

Hypercalcemia accompanied by a metabolic alkalosis (increased serum bicarbonate levels) represent hallmark laboratory findings in MAS. Co-existing renal dysfunction, as evidenced by an increase in serum creatinine, is common. Regulatory hormones including PTH and vitamin-D (1,25-OH vitamin D) are often appropriately suppressed. The presence of hypercalcemia in the setting of normal phosphorus, PTH and 1,25-OH vitamin D levels is one way that MAS can be differentiated from other causes of elevated calcium such as hyperparathyroidism.

Withdrawal of the source of calcium and alkali is often sufficient to cause resolution of symptoms. In addition to correcting dehydration, intravenous fluid administration promotes calciuresis and facilitates resolution of metabolic alkalosis. In acute MAS, after the offending agents are discontinued, calcium levels normalize within several days followed by resolution of headache, nausea, vomiting and dizziness and subsequent improvement in renal function. Patients with severe forms of MAS tend to experience more prolonged resolution of hypercalcemia and symptoms such as muscle aches. In some cases, several months may be required for calcium levels to normalize after calcium and alkali therapy has been discontinued *(Metab Case Rep. 2018;2018:18-0075*). Renal dysfunction is less likely to return to baseline in patients with more prolonged forms of MAS, and up to one third of patients can develop permanent renal impairment due to persistent hypercalcemia. Patients with severe manifestations of hypercalcemia such as coma and cardiac arrhythmias may require acute management with hemodialysis to more rapidly correct serum calcium levels.

Did you know?

Milk-alkali syndrome (MAS) is estimated to be responsible for 8-38% of hospital admittances for hypercalcemia.

MAS is the 3rd leading cause of hypercalcemia-related admissions behind hyperparathyroidism and hypercalcemia of malignancy. The increased use of calcium and vitamin-D-containing supplements by post-menopausal women for treatment and prevention of osteoporosis is thought to have recently contributed to a re-emergence of this syndrome *(J Am Soc Nephrol. 2010; 21(9):1440-3).*

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