Hypercaldemia and Alkalosis Due to the Milk-Alkali Syndrome: A Case Report and Review

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At one time, when antacids were the primary medical means of treating peptic ulcer disease, the milk-alkali syndrome was not an uncommon cause of hypercalcdemia. The simultaneous occurence of hypercalcdemia, alkalosis, and renal failure, in conjunction with the appropriate history of ingestion of antacids, was suggestive of the syndrome. With the advent of antisecretory therapy, however, the milk-alkali syndrome has become an uncommon diagnosis. I report a case of milk-alkali syndrome and review the history of this syndrome as reported in the medical literature. Contemporary reports have focused on understanding the pathophysiology of the syndrome. Recent series have indentified a shifting demographic profile, as increasing numbers of elderly women consume calcium carbonate as an anti-osteoporosis measure.

INTRODUCTION

Milk-alkali syndrome (hypercalcdemia and alkalosis associated with the ingestion of large amounts of antacid containing calcium and absorbable alkali) was at one time a somewhat regular cause of hypercalcdemia, particularly in men with symptoms of peptic ulcer disease. However, knowledge of its etiology, and more recently the development of anti-secretory therapy for peptic ulcer disease, have caused this diagnosis to relegated to the "rare" among those processes included in the differential diagnosis of hypercalcdemia. I describe a case of milk-alkali syndrome caused by excess ingestion of calcium carbonate, and review the literature, chronologically highlighting significant reports and studies of this syndrome from the early twentieth century until the present. Some recent literature suggests that the incidence of milk-alkali syndrome may be rising in new patient populations.

CASE REPORT

A 66 year old white male was brought by his friends to Jacobi Medical Center after becoming lethargic and distressed in a social club. The patient, whose past medical history included ethanol abuse, had been feeling ill for approximately three weeks. Over that time, according to his wife, he had been nauseated, anorectic and constipated, and had had some occasional vomiting. Additionally, the patient had been consuming large amounts of laxatives, TumsTM and RolaidSTM daily. His diet had consisted mainly of EnsureTM during this period of anorexia. During the week prior to admission, his symptoms worsened and he became pale. On the day of admission, the patient went to jury duty in the morning, but excused himself during the day because he felt ill. In the late afternoon, he attended a social club (American Legion) where he had, by his report, two or three beers. Over the course of the afternoon and evening, his friends noted that he became lethargic, distressed and clutched his chest, and at their insistence, he agreed to come to the Emergency Department.

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His past medical history included cataract surgery two years prior to admission, and a hospitalization 18 years prior to admission for a questionable myocardial infarction; details of this admission were vague and there was little evidence to suggest coronary artery disease. Additionally, the patient had a history of ethanol abuse. His wife reported that prior to his retirement 2 years ago, he would drink in the evenings at the social club, and at home as well; she estimated his daily beer consumption at 10 cans. She stated that his drinking did not interfere with his work, managerial in nature, but that his drinking had increased since retirement and she denied that he had any episodes of ethanol withdrawal. The patient’s ethanol consumption had decreased while he felt unwell over the weeks prior to admission. He reported taking no medications other than the antacids previously mentioned.

In the Emergency Department, he was afebrile, with a heart rate of 98 beats per minute, blood pressure of 108/58 mm Hg, and a respiratory rate of 12 breaths per minute. He was alert and fully oriented, and his physical exam revealed no abnormalities.

### Table 1. Initial hematologic and blood chemistry studies.

| Test (unit)                  | Value         |
|------------------------------|---------------|
| Hemoglobin (mg/dl)           | 10.4          |
| MCV (mm³)                    | 105.8         |
| White-cell count (per ml)    | 19,000, 87 % granulocytes |
| Erythrocyte Sedimentation Rate (mm/hr) | 124 |
| Sodium (meq/l)               | 133           |
| Potassium (meq/l)            | 3.2           |
| Chloride (meq/l)             | 76            |
| Carbon Dioxide (meq/l)       | 33            |
| Urea Nitrogen (mg/dl)        | 56            |
| Creatinine (mg/dl)           | 5.7           |
| Glucose (mg/dl)              | 100           |
| Calcium (mg/dl)              | 17.8          |
| Magnesium (mg/dl)            | 1.9           |
| Phosphate (mg/dl)            | 2.4           |
| Urate (mg/dl)                | 11.2          |
| Albumin (mg/dl)              | 3.9           |
| Total Protein (mg/dl)        | 7.5           |
| Arterial pH                  | 7.54          |
| pCO₂ (mm Hg)                 | 49            |
| pO₂ (mm Hg)                  | 94            |
| Osmolality (mosm/kg)         | 324           |
| Ethanol (mg/dl)              | 135           |

Amylase, Lipase, Lactate Dehydrogenase, Creatine Kinase, Alkaline Phosphatase, and transaminase activities were within normal limits

Significant admission laboratory studies are summarized in Table 1; his urea nitrogen and creatinine were normal at the time of his cataract surgery two years ago.

His chest X-ray showed a possible right upper lobe infiltrate, and his electrocardiogram showed ST-segment depressions in leads V3 and V4. Because of the history of chest-clutching and the cardogram findings, he was admitted to the Cardiac Care Unit. He was hydrated and given thiamine, folate, phosphate, potassium and magnesium supplements. Serial measurements of serum creatine kinase were within normal limits. With hydration,
hormone-related.

**DISCUSSION**

In 1912, Sippy introduced a milk and antacid (calcium carbonate, sodium bicarbonate, magnesium oxide, and bismuth subcarbonate) treatment for peptic ulcer disease [1]. Although “Sippy powders” proved to have some efficacy in relief of peptic ulcer symptoms, eleven years later, Hardt and Rivers described a syndrome of irritability, headache, dizziness, nausea, vomiting, myalgia, weakness and apathy in 16 of 32 patients undergoing the Sippy regimen, compared to 16 patients taking only milk [2]. These symptoms were associated with elevated serum urea nitrogen and bicarbonate, proteinuria and pyuria. Most of their patients recovered quickly after cessation of therapy, although one died of “subacute nephritis.” In 1934, Cope reported six new cases and found an elevation of serum calcium, magnesium and phosphate in these patients, who had altered mental status, vomiting, polyuria, myalgia and conjunctivitis [3]. The severity of alkalosis and hypochloremia was observed to worsen with age in these patients, with hemorrhage, vomiting, gastric aspiration and pre-existing renal impairment factors [4]. Burnett and colleagues described a more severe syndrome, with prolonged, excessive intake of milk and absorbable alkali, hypercalcemia, azotemia, proteinuria, alkalosis and calcinosis, without
hypercalciuria or elevated serum alkaline phosphatase [5]. Calcifications were found in the conjunctiva (band keratopathy), central nervous system, lymph nodes, vasculature and subcutaneous tissue. Withholding milk and alkali resulted in the return of serum calcium to normal values, hypophosphatemia and partial improvement in renal failure, although four of the six reported patients died.

McMillan and Freeman studied the syndrome by randomly assigning 40 men (most of whom had a history of peptic ulcer disease) to receive 6 ounces milk and either 3.6 g calcium carbonate or 15 ml of aluminum hydroxide or aluminum magnesium hydroxide, every two hours while awake (per day averages: 1.5 liters milk, 28 g calcium carbonate, 116 ml aluminum hydroxide or aluminum magnesium hydroxide) [6]. Serum levels of calcium, phosphate, creatinine and bicarbonate rose significantly in the calcium carbonate group compared to the aluminum or magnesium hydroxide group, as did urinary calcium. One patient developed symptoms of the syndrome, with marked elevations in serum calcium, phosphate, urea nitrogen, creatinine and bicarbonate; his symptoms and laboratory abnormalities subsided after discontinuation of milk and calcium carbonate.

Milk-alkali syndrome (hypercalcemia, alkalosis and renal failure due to ingestion of calcium, absorbable alkali and milk) was initially thought to comprise three distinct entities: an acute syndrome, as described by Hardt and Rivers in 1923, the chronic, severe "Burnett’s syndrome," and the intermediate "Cope’s syndrome." A history of milk and alkali ingestion, nausea, vomiting, lethargy, mental status changes and myalgias, elevated serum calcium, creatinine, and urea nitrogen, and normal to elevated phosphate and bicarbonate were shared features. The acute syndrome was thought to arise after short-term treatments and to resolve rapidly after withdrawal of milk and alkali, the subacute syndrome after intermittent, long-term milk/alkali treatment with additional features of polydipsia, polyuria, conjunctivitis and occasional band keratopathy, and the chronic syndrome after continuous long-term therapy, with additional features of pruritis, polydipsia, polyuria, band keratopathy and soft tissue calcifications including nephrocalcinosis. In chronic patients, symptoms might improve with renal function remaining at least partially impaired.

More recently, pathophysiology of milk-alkali syndrome was reviewed [7]. Although high calcium intake lowers 1,25 dihydroxy-vitamin D levels, there is wide variability in the fraction of calcium that is passively absorbed from the gastrointestinal tract in the absence of 1,25 dihydroxy-vitamin D, and a subgroup of individuals will have a high fractional absorption of calcium despite a large dietary calcium load and suppression of 1,25 dihydroxy-vitamin D. In the presence of any impairment in renal calcium excretion, these individuals will become hypercalcemic. Additionally, alkalosis likely compromises renal calcium excretion. However, alkalosis should not be expected from the relatively small alkali load in calcium carbonate consumption, since massive loads of sodium bicarbonate do not cause significant changes in systemic pH in normal individuals. However, several factors limit bicarbonate excretion during calcium carbonate ingestion: increased calcium causes increased sodium and free water excretion, which may cause volume depletion and consequently, increased proximal tubule bicarbonate reabsorption; parathyroid hormone suppression as well as direct tubular effects of calcium may also increase bicarbonate reabsorption. Thus other factors leading to volume contraction (vomiting, gastric aspiration, hemorrhage, thiazide diuretics), alkalosis (vomiting, gastric aspiration, hypokalemia), or impaired calcium clearance (pre-existing renal disease, volume contraction, thiazide diuretics) act to predispose a patient to the development of the milk-alkali syndrome.

The renal dysfunction of the milk-alkali syndrome results from multiple factors: hypercalcemia can directly cause a decrease in glomerular filtration rate and creatinine clearance, and dehydration contributes to renal impairment. Moreover, hypercalcemia and
alkalosis, especially if there is hyperphosphatemia due to suppression of parathyroid hormone, can lead to nephrocalcinosis and significant, irreversible defects in renal function. Understanding the pathophysiology of milk-alkali syndrome has made clear that there are not three distinct entities, but rather a continuum of disease that is fully reversible in the early stages but over time, with increasing soft tissue calcification, becomes irreversible and is associated with renal failure and poor outcomes.

Abreo and coworkers examined hormonal parameters in a recent series [8]. Despite heterogeneity of presentation, all five had been consuming large doses of calcium and absorbable alkali, and they had remarkably similar admission laboratory values: on average, calcium 13.5 mg/dl, phosphate 1.5 mmol/l, bicarbonate 39 meq/l, pH 7.55 and creatinine 7.6 mg/dl. Measurement of 1,25 dihydroxy-vitamin D in four patients revealed low values in two and low-normal values in two. Although paradoxically elevated parathyroid hormone levels in milk-alkali syndrome had been previously reported, Abreo and coworkers emphasize the need for determination of the N-terminus parathyroid hormone fragment in these patients, as the C-terminus fragment is dependent upon glomerular filtration for removal: in their patients, C-terminus parathyroid hormone was elevated, as expected, while in four of five patients, N-terminus parathyroid hormone was low or low-normal. The patient with an elevated N-terminus parathyroid hormone was suspected to have secondary hyperparathyroidism as a result of renal failure, in addition to the milk-alkali syndrome.

As the use of massive doses of calcium carbonate for the treatment of peptic ulcer disease has faded, the demographics of the disease has shifted. By 1982, patients who developed the syndrome were consuming lower doses of calcium carbonate (5 to 10 g daily) and had predisposing factors such as pyloric obstruction, vomiting, hemorrhage, hypokalemia, hypertension, pre-existing renal disease and use of thiazide diuretics [7]. More recently, Kapsner and coworkers further shifted the demographics in their study of cardiac transplant patients treated with long-term calcium carbonate to prevent corticosteroid-associated peptic ulcer disease and osteoporosis [9]. They reviewed data from 297 transplant recipients receiving between 3.2 to 12 g calcium carbonate per day for up to one year, and reported that 65 had serum calcium levels over 10.7 mg/dl. Of the hypercalcemic patients, 31 were also alkalotic and 37 had evidence of renal impairment. The authors noted that the incidence of milk alkali syndrome may increase given the popularity of recommending calcium supplementation for the prevention and treatment of osteoporosis. In another study, Beall and Scofield recently reported three cases of milk-alkali syndrome, and reviewed all patients admitted with hypercalcemia to the University of Oklahoma Medical Center between January 1985, and December, 1993 [10]. They found seven of 100 patients who fit the criteria for milk-alkali syndrome on the basis of increased consumption of calcium and absorbable alkali, hypercalcemia, metabolic alkalosis, and absence of other cause for hypercalcemia. The laboratory profile of these patients was similar to those of Abreo et al. [8]: calcium 14.6 mg/dl, phosphate 2.9 mg/dl (four of seven subjects were hypophosphatemic and one of seven was hyperphosphatemic), bicarbonate 31 meq/l (four of seven subjects had bicarbonate levels of 28-29 meq/l), and creatinine 2.1 mg/dl (three of seven had normal creatinine levels). Of the six patients in which it was measured, parathyroid hormone was low in three and low-normal in three. After treatment for hypercalcemia, one patient developed marked, symptomatic hypocalcemia with high parathyroid hormone levels, and another developed asymptomatic hypocalcemia. The authors attributed this to suppression of parathyroid hormone, for in the milk-alkali syndrome, unlike hyperparathyroidism or malignancy-related hypercalcemia, there is no stimulus for calcium absorption from bone as the hypercalcemia is treated. They found that recent reports of milk-alkali syndrome have neither been associated with hyperphosphatemia nor with ingestion of large quantities of milk (a source of dietary phosphate).
These authors also noted that this syndrome may become more common as increasing numbers of women are taking calcium carbonate for treatment or prevention of osteoporosis.

The case we have described is typical of the traditional presentation of milk-alkali syndrome. The patient presented with a history of ingestion of large quantities of calcium carbonate-containing antacids, and additionally had been vomiting, causing both volume contraction and further alkalosis, increasing his risk. Serum chemistries revealed the triad of hypercalcemia, alkalosis and renal failure. More common causes of hypercalcemia, which must be excluded to confirm the diagnosis, were not found: there was no evidence of multiple myeloma or other malignancy, and parathyroid hormone was suppressed, ruling out primary hyperparathyroidism. After being hydrated the patient became hypocalcaemic, a phenomenon described previously by Beall and Scofield [14]. This rebound hypocalcaemia is likely a consequence of suppression of the parathyroid, which cannot respond immediately to the rapid lowering of serum calcium achieved by hydration in these patients. This results in a lag time before secretion of parathyroid hormone and stimulation of calcium resorption from bone. In order to avoid rebound hypocalcemia in patients suffering from the milk-alkali syndrome, perhaps gentle hydration is preferable, in contrast to the vigorous hydration required in hyperparathyroidism and malignancy-related hypercalcemia. Additionally, cautious use of calcium supplementation when serum calcium levels fall into the normal range may be justified. Finally, a more physiologically elegant solution would be to administer parathyroid hormone to these patients as serum calcium levels begin to fall. Although the patient’s hypercalcemia and other electrolyte disturbances responded to hydration and supplementation with potassium and eventually calcium, and despite his improving renal function, his condition deteriorated, related to the development of an aspiration pneumonia then sepsis thought unrelated to the milk-alkali syndrome.

This patient fit the picture of one who has classically developed milk-alkali syndrome in that he was a male, ingesting antacid for relief of dyspeptic symptoms. However, as emphasized by the recent literature devoted to this subject [7-10], the demographics of the syndrome are shifting as other patient populations take dietary calcium supplements, particularly as an anti-osteoporosis measure. This emphasizes the need for a careful medication history, including over-the-counter medications. For anyone presenting with hypercalcemia, a direct inquiry regarding the use of antacids or calcium supplements will, in most cases, rule out milk-alkali syndrome; occasionally, there will be a history of calcium carbonate ingestion, and this history may alter the evaluation of the patient.

As the risk of developing milk-alkali syndrome is hypothesized to be related in part to vitamin-D independent intestinal calcium absorption, it is difficult to know which patients are at risk. It is also unknown if concurrent use of vitamin D or activated vitamin D increases the likelihood of developing milk-alkali syndrome by stimulating intestinal calcium absorption in the absence of an endogenous, physiologic stimulus. It is clear that patients with renal insufficiency or volume contraction also have a higher risk, raising the possibility that for these patients, a lower daily dose or an alternate-day dosing schedule would reduce their risk. Monitoring serum calcium levels may be useful since calcium levels are elevated prior to irreversible renal damage.

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