Health-Behavior Induced Disease: Return of the Milk-Alkali Syndrome

Joseph B. Caruso, MD, Rajendrakumar M. Patel, MD, Karan Julka, MD, and David C. Parish, MD, FACP

Department of Internal Medicine, Mercer University School of Medicine, 707 Pine Street, Macon, GA, 31201, USA.

The milk-alkali syndrome is a well-documented consequence of excessive calcium and alkali intake first recognized in association with early 20th century antacid regimens. The syndrome became rare after widespread implementation of modern peptic ulcer disease therapies. With recent trends in osteoporosis therapy coupled with widely available calcium-containing supplements, the milk-alkali syndrome has reemerged as an important clinical entity. Our case illustrates a patient who self-medicated his peptic ulcer disease with a regimen resembling a common early 20th century dyspepsia regimen. When superimposed upon chronic high calcium supplementation, the patient became acutely ill from the milk-alkali syndrome. When taken to excess, or used inappropriately, medications and supplements ordinarily considered beneficial, can have harmful effects. Our case underscores the importance of obtaining a thorough medication history including use of over-the-counter supplementation.

KEY WORDS: milk-alkali syndrome; health behavior; hypercalcemia; calcium supplementation.
DOI: 10.1007/s11606-007-0226-0
 2007;22:1053–1055

INTRODUCTION

The milk-alkali syndrome, a triad of hypercalcemia, metabolic alkalosis, and renal insufficiency, was identified in 1923 as an adverse effect of peptic ulcer disease therapies involving the use of dairy products and alkaline powders.[1] Such treatments, heralded as a "medical cure" for gastric and duodenal ulcers by Sippy[2] in 1915, confined patients to bed rest for weeks and called for the hourly feeding of milk and creamed products with powders of "heavy calcined magnesia," sodium bicarbonate, and "bismuth subcarbonate" administered between each feeding. Subsequent research reported the onset of toxic symptoms from 4 days to 4 weeks after starting the regimen.[1]

By 1985 with the widespread use of proton-pump inhibitors and antibiotic therapies for peptic ulcer disease, the milk-alkali syndrome essentially disappeared, accounting for less than 1% of hypercalcemia cases.[3,4] However, now, the syndrome has again risen in clinical importance as the third most common cause of hypercalcemia behind malignancy and primary hyperparathyroidism.[3,4] Recent trends in the prevention and treatment of osteoporosis using widely available over-the-counter (OTC) calcium supplements appear to be contributing to its return.[4] Physicians must be aware of the potential use of OTC agents by the health-seeking individual and should consider the possibility that multiple calcium-containing agents are being consumed simultaneously by the hypercalcemic patient.

Received November 9, 2006
Revised April 11, 2007
Accepted April 16, 2007
Published online May 5, 2007

CASE REPORT

A 60-year-old male had been experiencing confusion, generalized weakness, difficulty ambulating, vomiting, and a decreased oral intake worsening over the 5 days before admission. The patient consumes more than two grams of calcium carbonate daily using OTC nutritional supplements, in addition to milk and 800 IU vitamin D supplements, which he ingests for the purpose of osteoporosis prevention. In addition, the patient suffers from recurrent gastrointestinal pain and remedies his dyspepsia with one teaspoon of sodium bicarbonate powder and unknown quantities of calcium carbonate and aluminum/magnesium hydroxide antacids during acutely painful episodes. Before admission, the patient had been using an unspecified amount of calcium carbonate-containing antacids in addition to his usual amount of nutritional supplements.

Physical examination demonstrated a dehydrated male, mildly confused but without other neurological disturbances. Laboratory data showed a serum bicarbonate level of 33 meq/L (22–32 meq/L), serum albumin-corrected calcium level of 12.3 mg/dL (8.5–10.2 mg/dL), serum phosphorus of 3 mg/dL (2.5–4.8 mg/dL), serum blood urea nitrogen of 37 mg/dL (5–22 mg/dL), and a creatinine level of 6 mg/dL (0.5–1.4 mg/dL) with a pH of 7.562 and pCO2 of 39.8 mmHg obtained by an arterial blood gas. A review of records showed the patient's albumin-corrected calcium level was 9.72 mg/dL approximately 6 months previously with a creatinine level of 1.1 mg/dL at that time. The patient's thoracic radiograph was normal, and he had no history of malignancy, sarcoidosis, or lithium therapy. A serum intact PTH (iPTH) level was low at 7 pg/mL.

The patient was admitted for hypercalcemia, acute renal insufficiency, and metabolic alkalosis and underwent saline diuresis, with clearing of his mentation overnight, and improvement of the pH (7.476) by the third hospital day and normalization of the serum albumin-corrected calcium

(9.88 mg/dL) on the sixth hospital day. Serum creatinine steadily trended downward to 2.6 mg/dL on the day of discharge and the patient left our institution in stable condition.

DISCUSSION

The milk-alkali syndrome is classically defined as a triad of hypercalcemia, metabolic alkalosis, and renal insufficiency.[5] To manifest the syndrome, calcium is consumed orally together with an absorbable alkali, such as calcium carbonate antacids.[6] Hypercalcemia typically develops when calcium carbonate consumption exceeds 5 g per day, (or 3 g per day if underlying renal insufficiency is present).[7] Hypercalcemia tends to induce emesis and natriuresis, both of which result in volume loss. This volume loss contributes to the alkalotic state by inducing an increase in proximal tubular bicarbonate reabsorption. In addition, high serum calcium levels worsen the alkalosis through suppression of parathyroid hormone (PTH) by negative feedback.[7] It is a normal function of PTH to inhibit proximal tubular bicarbonate reabsorption. Therefore, whenever PTH is suppressed, bicarbonate is reabsorbed such that calcium and bicarbonate both impede the excretion of each other.[3,5] A vicious cycle ensues when volume depletion and renal vasoconstriction reduce the glomerular filtration rate (GFR), and consequently, reduce the calcium clearance.[7] With reduced renal function, the alkalotic state is maintained in the setting of high calcium and alkali gastrointestinal absorption.[5]

Clinically, the milk-alkali syndrome is described in terms of three different forms representing the progressive stages of the milk-alkali syndrome: the acute form, "toxemia"; the intermediate, "Cope's syndrome"; and the chronic form, "Burnett's syndrome". The acute form manifests within 2 to 30 days after consumption of calcium and absorbable alkali and consists of irritability, vertigo, apathy, headache, weakness, myalgia, and vomiting, largely related to the presence of hypercalcemia and metabolic alkalosis.[5] Recovery from the acute form usually occurs within 1–2 days after cessation of calcium and alkali ingestion. Intermediate milk-alkali syndrome occurs within several weeks of calcium and alkali ingestion,[6] but may also result from chronic intermittent ingestion.[5] Manifestations are similar to the acute form but also include conjunctivitis from calcium salt deposition. Symptomatic improvement occurs over the course of weeks as opposed to days compared to the acute form.[5] Milk-alkali syndrome, in its chronic form, exists when soft tissue calcifications are present, resulting in conjunctivitis, band keratopathy of the cornea, musculoskeletal deposits, and nephrocalcinosis.[5] The renal damage in chronic milk-alkali syndrome is thought to be irreversible.[5]

The preferred laboratory evaluation of hypercalcemia is by measure of the albumin-corrected calcium or by the ionized serum calcium, with abnormal values confirmed by a repeat measure.[3] Serum urea nitrogen and creatinine measurements demonstrate renal insufficiency.[8] Simultaneous measurement of the arterial blood gas data and serum chemistries confirm the presence of a metabolic alkalosis. Additional biochemical derangements such as hypochloremia and hypokalemia may be variable, but when present, further suggest the diagnosis of milk-alkali syndrome.[5] Interestingly, hyperphosphatemia was documented in older reports of the milk-alkali syndrome as a result of the high phosphorus load in milk and impaired phosphorus excretion resulting from reduced renal function in general.[6] More recent cases of the syndrome do not feature high phosphorus levels as ingestion of milk is no longer a common precipitating factor.[6]

The clinician should pursue other causes of hypercalcemia such as granulomatous diseases, lithium toxicity, diuretic use, vitamin A and/or D intoxication, adrenal insufficiency, and hyperparathyroidism.[3] Measurement of iPTH will reveal primary hyperparathyroidism. In the milk alkali syndrome, the iPTH is usually suppressed.[8] In one report, 11% of milk-alkali syndrome patients were misdiagnosed with primary hyperparathyroidism and underwent unnecessary surgical exploration of the parathyroid glands.[8] Consideration of the milk-alkali syndrome as the cause of hypercalcemia can eliminate such unnecessary procedures.

Given the readily available OTC calcium preparations on the market and the recent emphasis on osteoporosis prevention and treatment[4,8] an extensive medication and dietary history is required to screen for multiple calcium-containing agents, which may be contributing to an acute hypercalcemic event. Although calcium carbonate products are common causes of the milk-alkali syndrome because they contain both a calcium component and an absorbable alkali component,[8] ingestion of a calcium source concurrently with any other type of absorbable alkali could potentially result in the milk-alkali syndrome.[5] Aside from the over-use of antacid regimens and misuse of OTC nutritional supplements, cultural practices and psychopathological behaviors should also be considered.[9] For example, in Asia and Africa, the milk-alkali syndrome has been associated with the ancient practice of chewing "betel quid," which is a nut of the *Areca catechu* "betel palm" treated with a calcium hydroxide lime paste and chewed for its psychogenic effects by approximately 200 million people worldwide.[10,11] Massive cheese ingestion can result in the "cheese alkalosis syndrome" described in a Swedish report of an anorexic/bulimic patient with a pica syndrome for cheese who required multiple hospitalizations.[12] Another account describes an anorexic–bulimic patient who developed a "Rolaids-yogurt syndrome" after chronic daily consumption of 1,700 mg of calcium-containing Rolaids tablets and yogurt.[7] Milk-alkali in the setting of Munchausen's syndrome has also been documented in a malingering patient after the physician discovered calcium carbonate tablets and diuretics within a hidden compartment in the patient's purse.[13]

Therapy for the milk-alkali syndrome involves limiting calcium and alkali ingestion, specifically, a reduction of total daily calcium carbonate intake to 3–3.375 g (the equivalent of a daily elemental calcium intake to 1.2–1.5 g).[4] In cases where calcium supplementation is required, it is recommended to consume calcium without absorbable alkali.[8] Initial treatment of hypercalcemia is volume expansion with intravenous saline. Adjunctive measures involve enhancing calcium excretion with loop diuretics, while monitoring intake, urinary volume, and electrolyte values.[3,4] In refractory cases, hypocalcemic agents may also be employed, such as calcitonin and/or bisphosphonates.[3] In cases of chronic milk-alkali syndrome, improvement in hypercalcemia and renal insufficiency may occur over a prolonged period; hemodialysis may be needed in severe cases.[5] Typically, hemodialysis is reserved for hypercalcemia levels above 18 mg/dL refractory to rehydration, saline

diuresis, and calcitonin.[3] Renal recovery occurs slowly, with improvement in serum creatinine levels occurring over the course of a week in one reported case.[7]

CONCLUSION

The milk-alkali syndrome, once a common clinical manifestation from dyspepsia regimens, has reemerged as a toxic effect of excessive calcium supplementation and osteoporosis treatments. Our case is interesting because it involves the use of sodium bicarbonate and milk in conjunction with over-the-counter calcium supplements and antacids, and as such, approximates the components of Sippy's dyspepsia regimen, which caused this syndrome to be identified nearly a century ago. In the case report described above, the patient became acutely ill from hypercalcemia as a result of the combined effects of acute antacid use together with the consumption of his usual daily calcium supplements. Our case illustrates the need to take a complete medication and dietary history to screen for multiple sources of calcium intake. Cultural practices and psychopathologic behavior may also be factors. Clearly, as our case illustrates, potential harm sometimes results from aggressive health-seeking behavior. This is especially true when such behavior is combined with excessive intake of certain foods, pharmaceuticals, and nutritional supplements which, when taken in excess, may lead to unintended deleterious effects.

Conflict of Interest Statement: *None disclosed.*

Corresponding Author: *Rajendrakumar M. Patel, MD; Department of Internal Medicine, Mercer University School of Medicine, 707 Pine Street, Macon, GA, 31201, USA (e-mail: pateraj@gmail.com).*

REFERENCES

1. **Cooke AM.** Alkalosis occurring in the alkaline treatment of peptic ulcers. Quart J Med. 1932;25:527.
2. **Sippy BW.** Gastric and duodenal ulcer: medical cure by an efficient removal of gastric juice corrosion. JAMA. 1915;64:1625.
3. **Grundfast MB, Still CD, Komar MJ.** Hypercalcemia and peptic ulcer disease-related milk-alkali syndrome. Nutr Clin Prac. 2003.
4. **Gordon MV, Hamblin PS, McMahon LP.** Life-threatening milk-alkali syndrome resulting from antacid ingestion during pregnancy. MJA. 2005;182(7):350–1.
5. **Orwoll ES.** The milk-alkali syndrome: current concepts. Ann Intern Med. 1982;97:242–8.
6. **McMillan DE, Freeman RB.** The milk alkali syndrome: a study of the acute disorder with comments on the development of the chronic condition. Medicine. 1965;44:485–501.
7. **Muldowney WP, Mazbar SA.** Rolaids-yogurt syndrome: a 1990s version of milk-alkali syndrome. Am J Kidney Dis. 1996;27(2):270–2.
8. **Beall DP, Scofield RH.** Milk-alkali syndrome associated with calcium carbonate consumption. Medicine. 1995;74:89.
9. **Jacobs TP, Bilezikian JP.** Rare causes of hypercalcemia. J Clin Endocrinol Metab. 90(11):6316–22.
10. **Wu K, Chuang R, Wu FL, et al.** The milk-alkali syndrome caused by betelnuts in oyster shell paste. Clin Toxicol. 1996;34(6):741–5.
11. **Norton SA.** Betel: consumption and consequences. J Clin Endocrinol Metab. 1998;38(1):81–8, Jan.
12. **Kallner G, Karlsson H.** Recurrent factitious hypercalcemia. Am J Med. 1987;82:536–8.
13. **Frame B, Jackson G, Kleerekoper M, Rao D, DeLorenzo A, Garcia M.** Acute severe hypercalcemia a la Munchausen. Am J Med. 1981;70:316–9.