

CASE REPORT

Hypercalcemia and Acute Renal Failure in Milk-Alkali Syndrome: A Case Report

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Historically, the milk-alkali syndrome developed as an adverse reaction to the Sippy regimen of milk, cream and alkaline powders as treatment for peptic ulcer disease. The classic description includes hypercalcemia, metabolic alkalosis, and renal failure. Over the past 20 years, milk-alkali syndrome has had a resurgence, as consumption of supplements containing calcium has increased. A 46-year-old man presented to the emergency department after outpatient labs to evaluate his fatigue. He was found to have acute renal failure and hypercalcemia (total serum calcium was 15.9 mg/dL). Subsequent laboratory evaluation excluded both hyperparathyroidism and malignancy as causes. A detailed history led to the diagnosis of milk-alkali syndrome. With hydration and cessation of calcium carbonate ingestion, his renal function and serum calcium levels returned to normal. Physicians should have a high index of suspicion for milk-alkali syndrome in patients with hypercalcemia. Milk-alkali syndrome is no longer a merely a historical curiosity; it is currently the third most common cause of hypercalcemia. *Journal of Hospital Medicine* 2010;5:E18–E20. © 2010 Society of Hospital Medicine.

KEYWORDS: hypercalcemia, milk-alkali, renal failure.

Historically, the milk-alkali syndrome developed as an adverse reaction to the Sippy regimen of frequent feedings of milk, cream, and alkaline powders as treatment for peptic ulcer disease.¹ The classic description includes hypercalcemia, metabolic alkalosis, and renal failure. This syndrome seemingly disappeared when modern acid suppression therapies such as histamine-2 blockers and proton pump inhibitors improved dyspepsia treatment. Over the past 20 years, milk-alkali syndrome has had a resurgence, as consumption of supplements containing calcium has increased.² Calcium carbonate supplements are a popular over-the-counter treatment for osteoporosis, dyspepsia, hypocalcemia, and hyperphosphatemia; these supplements provide both the calcium and alkali required for the development of milk-alkali syndrome.

A 46-year-old man presented to the emergency department after his physician ordered outpatient laboratory tests to evaluate his fatigue. The patient was found to have acute renal failure and hypercalcemia. His serum creatinine was 3.6 mg/dL, increased from his baseline of 1.1 mg/dL several months prior, and his serum calcium was 14.9 mg/dL. Ten days prior to admission he developed increasing fatigue, decreased appetite, and decreased urine output, which he attributed to recent manual labor during summer. He reported taking an occasional calcium carbonate (Tums) for dyspepsia. He did not report pain or other complaints.

His medical history included hypertension and hyperlipidemia. He had a colonoscopy 1 year prior to presentation that was significant for a high-grade dysplastic polyp and was currently due for repeat colonoscopy. His medications included clonidine, lisinopril, and aspirin. He had no recent medication changes. He had a 30 pack/year history of cigarette smoking and drank occasionally.

On physical exam, his temperature was 99.8°F, blood pressure 97/48 mmHg, heart rate 89 beats per minute, respirations 20 breaths per minute, with a room air saturation of 97%. He had dry mucus membranes and the remainder of the physical exam was unremarkable.

In the emergency department laboratory testing revealed a creatinine of 4.6 mg/dL, serum total calcium of 15.9 mg/dL, serum bicarbonate level of 26 mmol/L, phosphate of 3.9 mg/dL, albumin of 4.4 gm/dL, and alkaline phosphatase of 92 IU/L. The urine specific gravity was 1.019 gm/mL (see Table 1 for the patient's complete admission laboratory values).

His intact parathyroid (PTH) hormone was 18.8 pg/mL (normal, 15-65). PTH hormone-related peptide (PTHrP) was <2.5 pmol/L. After reviewing these laboratory test results, we proceeded with further questioning, during which he admitted to taking approximately 15 to 20 Tums (>7.5 gm of calcium carbonate) daily for dyspepsia rather than the occasional Tums he had originally reported. Over the next 3 days, his calcium decreased to 8.4 mg/dL and his creatinine decreased to 1.6 mg/dL with intravenous hydration. His fatigue improved. His 25-hydroxy vitamin D (25-OH-Vitamin D) level was 23 ng/mL (normal, 16-74 ng/mL).

At his 1 week follow-up, his calcium was 8.1 mg/dL, and his creatinine had returned to normal at 0.9 mg/dL. His intact PTH level was elevated at 240 pg/mL.

Discussion

Milk-alkali syndrome is now believed to be the third most common reason for hypercalcemia hospital admission.^{2,3} Malignancy and primary hyperparathyroidism are the only 2 causes of hypercalcemia more common than milk-alkali

TABLE 1. Laboratory Values

| | Result (Normal Range) |
|--|-----------------------|
| At admission | |
| Sodium (mmol/L) | 135 (135-145) |
| Potassium (mmol/L) | 4.4 (3.8-5.0) |
| Chloride (mmol/L) | 97 (98-107) |
| Bicarbonate (mmol/L) | 25 (22-31) |
| BUN (mg/dL) | 64 (9-20) |
| Creatinine (mg/dL) | 4.6 (0.5-1.5) |
| Calcium (mg/dL) | 15.9 (8.4-10.2) |
| Albumin (g/dL) | 4.4 (3.5-5.0) |
| Alkaline phosphatase (U/L) | 92 (38-126) |
| ALT (U/L) | 24 (11-66) |
| AST (U/L) | 17 (15-46) |
| Bilirubin, total (mg/dL) | 0.3 (0.3-1.2) |
| Ionized calcium (mmol/L) | 1.58 (1.13-1.32) |
| Creatinine kinase (U/L) | 83 (35-232) |
| WBC (thousands/cm ²) | 12.1 (4-11) |
| Hemoglobin (g/dL) | 16.5 (14-18) |
| Hematocrit (%) | 48.6 (40-54) |
| Platelets (thousands/cm ²) | 224 (150-350) |
| Intact PTH (pg/mL) | 18.78 (15-65) |
| PTHrP (pmol/L) | <2.5 (<5) |
| 25-OH-Vitamin D (ng/mL) | 23 (16-74) |
| <i>H. pylori</i> antibody | Negative |
| SPEP | No M-spike |
| UPEP | No M-spike |
| Hospital Day 4 (date of discharge) | |
| BUN (mg/dL) | 21 (9-20) |
| Creatinine (mg/dL) | 1.6 (0.5-1.5) |
| Calcium(mg/dL) | 8.4 (8.4-10.2) |
| WBC (thousands/cm ²) | 6.5 (4-11) |
| Hemoglobin (g/dL) | 14.1 (14-18) |
| Hematocrit (%) | 40.8 (40-54) |
| Day 10 (at follow-up) | |
| BUN (mg/dL) | 16 (9-20) |
| Creatinine (mg/dL) | 0.9 (0.5-1.5) |
| Calcium (mg/dL) | 8.1 (8.4-10.2) |
| Intact PTH (pg/mL) | 240 (15-65) |

Abbreviations: 25-OH-Vitamin D, 25-hydroxy vitamin D; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; M-spike, M-protein level spike; PTH, parathyroid; PTHrP, PTH hormone-related peptide; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; WBC, white blood cell count.

syndrome in hospitalized patients; these must be excluded before making a definitive diagnosis of milk-alkali syndrome. The differential diagnosis for hypercalcemia also includes other less common etiologies such as medications (hydrochlorothiazide and lithium), as well as familial hypocalciuric hypercalcemia, hyperthyroidism, Addison's disease, acromegaly, tertiary hyperparathyroidism, and vitamin D intoxication. Physicians often discover hypercalcemia incidentally on routine laboratory tests, and diagnostic workup should include a thorough history and physical examination, as well as further laboratory evaluation.

The diagnosis of milk-alkali syndrome requires a history of increased calcium and alkali intake, but is otherwise a

diagnosis of exclusion. Given the increasing consumption of nonprescribed calcium supplements, one should have a high index of suspicion for the diagnosis of milk-alkali syndrome, as patients may not consider calcium carbonate to be hazardous or even a medication and thus may not report calcium carbonate consumption. Patients often view calcium carbonate as a benign treatment for dyspepsia. Its over-the-counter availability and economical price make it a common self-treatment for minor dyspepsia or as prevention of osteoporosis. Calcium supplementation is increasingly added to many products, making it easy for patients to consume large quantities of calcium unknowingly. Of note, without the absorbable alkali supplied by the carbonate in calcium carbonate (Tums), milk-alkali syndrome does not occur. The amount of calcium carbonate necessary to cause milk-alkali syndrome is not well known, though it is speculated to be as little as 5 to 10 g of calcium in the form of calcium carbonate, especially in those with other risk factors for hypercalcemia such as chronic renal insufficiency or vomiting.² Workup of hypercalcemia should entail careful questioning about medications, as well as over-the-counter supplements, vitamins, and foods.

Manifestations of the milk-alkali syndrome include renal failure, metabolic alkalosis, and volume contraction. Normally, the kidneys prevent hypercalcemia by excretion of excess calcium. Hypercalcemia can cause tubular damage and vasoconstriction of the renal afferent arteriole leading to acute renal failure.^{2,4} Hypercalcemia can also cause nephrogenic diabetes insipidus, causing impaired renal concentrating ability, leading to increased sodium excretion and volume contraction.² In addition, alkalosis further impairs calciuresis.² Laboratory values usually reveal suppressed PTH and vitamin D levels due to hypercalcemia caused by exogenous intake of calcium.⁵ Hypercalcemia causes suppression of PTH, which can lead to hyperphosphatemia, as well as decreased conversion of vitamin D to the active 1,25-dihydroxyvitamin-D form.

The management of hypercalcemia due to milk-alkali syndrome is supportive and includes saline hydration as well as withholding calcium carbonate. Management of hypercalcemia due to malignancy and hyperparathyroidism includes bisphosphonates with the addition of calcitonin if symptoms are severe.^{6,7} There is no evidence that supports the use of bisphosphonates in the treatment of milk-alkali syndrome. Loop diuretics are sometimes used to promote calciuresis, though evidence is lacking to support this, and it may worsen renal failure.⁶

In this case, a middle-aged man took greater than the recommended dose of calcium carbonate for dyspepsia, which led to the development of acute renal failure and hypercalcemia. At first, the patient did not provide an accurate history of the extent of his calcium carbonate ingestion, leading us to focus on hyperparathyroidism or malignancy. With aggressive hydration and cessation of calcium carbonate, his renal function and serum calcium returned to baseline. Because we initially assumed occult malignancy as the

most likely diagnosis, we gave the patient pamidronate. The patient did not have a significant alkalemia (serum bicarbonate level was normal). This was thought to be due to the patient's degree of renal failure causing a concomitant metabolic acidosis. The patient's follow-up elevated PTH level may be explained by bisphosphonate administration or underlying primary hyperparathyroidism. Of note, decreasing calcium levels have also been speculated to be a cause of high PTH levels.⁸

In conclusion, physicians should have a high index of suspicion for milk-alkali syndrome in patients with hypercalcemia. Calcium carbonate is responsible for most cases of milk-alkali syndrome, and clinicians should inquire about the use of this supplement in all patients with hypercalcemia. Milk-alkali syndrome is no longer a merely a historical curiosity; it is currently the third most common cause of hospital admissions for hypercalcemia.

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