CASE IN POINT

MILK-ALKALI SYNDROME

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As an etiology of hypercalcemia, this syndrome had all but disappeared. Now it's resurfaced. This case illustrates why.

The first time milk-alkali syndrome was described as a cause of hypercalcemia was in the 1920s. It occurred in patients who ingested excessive amounts of milk or cream and used absorbable antacids, such as sodium bicarbonate.[1,2] Typically, affected patients reported taking elemental calcium in excess of 4 g/day.

Owing to better gastrointestinal ulcer treatments developed over the past several years, this syndrome had all but disappeared as an etiology of hypercalcemia—except in people taking very high doses of calcium, for example, to treat osteoporosis. By 1985, fewer than 1% of all hypercalcemia cases were attributed to milk-alkali syndrome.

Since 1990, however, there has been a resurgence of milk-alkali syndrome, which now accounts for up to 12% of all hypercalcemia cases, making it the third leading cause of hypercalcemia behind primary hyperparathyroidism and malignancy.[2] Here, I present a case in which the syndrome appears to have been triggered by excessive use of an over-the-counter antacid product and a mineral supplement.

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INITIAL EXAM

In June 2003, a 57-year-old white man, accompanied by his mother, presented to the emergency department with a four-week history of worsening confusion and ataxia. He was admitted to the medical intensive care unit with an abnormal electrocardiogram (ECG) and a serum calcium level of 21.4 mg/dL (normal, 8.5 to 10.1 mg/dL). A general physical examination revealed that he was somnolent and had orthostatic hypotension but was otherwise essentially normal.

He hadn't seen a physician for 30 years, though he reported having had severe dyspepsia for several years. He said he took no medication consistently except for over-the-counter antacid tablets containing calcium carbonate and mineral supplement tablets containing calcium, magnesium, and zinc—both of which he took in such large quantities that his total daily dose of elemental calcium averaged 24 g/day.

His ECG showed a shortened QT interval, sinus bradycardia with first-degree atrioventricular block, and intermittent junctional rhythm (Figure). Laboratory studies showed that he had low levels of serum sodium, 24-hour urinary calcium excretion, and intact parathyroid hormone and high levels of blood urea nitrogen, serum creatinine, and serum magnesium (Table). His chest-abdomen-pelvis computed tomography scan, serum protein electrophoresis, and urinary protein electrophoresis were all normal.

TREATMENT COURSE

He was diagnosed with milk-alkali syndrome, his calcium supplements were discontinued, and saline diuresis was initiated. By the seventh day after admission, his calcium level had fallen to 7.8 mg/dL, his ECG had normalized, and he had shown remarkable clinical improvement in mental status

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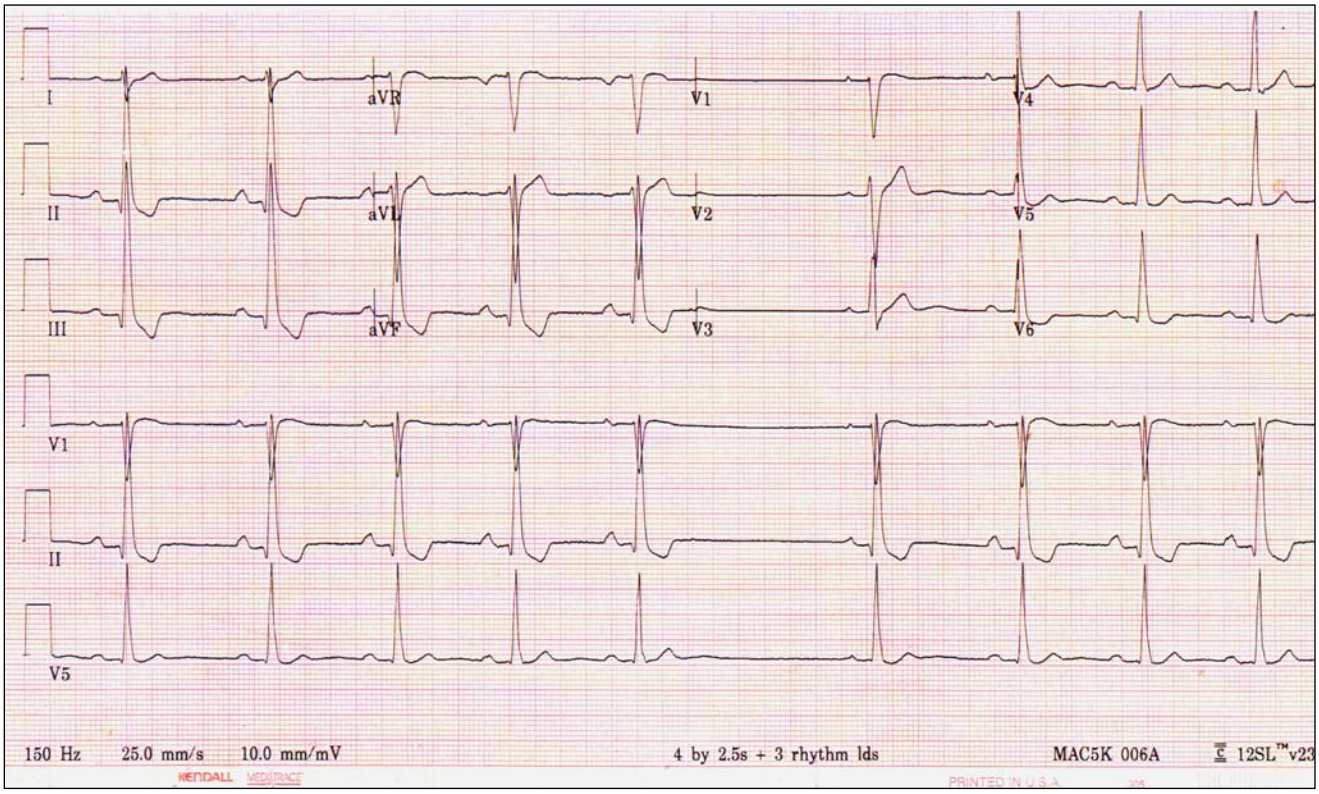

Figure. Patient's electrocardiogram showing a shortened QT interval, sinus bradycardia with first-degree atrioventricular block, and intermittent junctional rhythm.

and blood pressure. Three months later he remained clinically stable with a normal serum calcium level and a normal renal status.

ABOUT THE CONDITION

In susceptible individuals, milk-alkali syndrome begins with the development of hypercalcemia, which then leads to polyuria, polydipsia, dehydration, metabolic alkalosis, mental status changes, and prerenal reduction in the glomerular filtration rate. If these conditions persist, irreversible renal damage in the form of nephrocalcinosis may occur. In this chronic form, the disease is called Burnett syndrome.

These phenomena and perhaps some suppression of endogenous parathyroid hormone secretion due to mild hypercalcemia increase bicarbonate resorption and, in the face of continued calcium carbonate ingestion, lead to alkalosis. The alkalosis then exacerbates the hypercalcemia by selectively enhancing calcium resorption in the distal nephron.

A self-perpetuating cycle in which mild hypercalcemia causes bicarbonate retention followed by alkalosis and renal calcium retention, ultimately worsening the hypercalcemia and the alkalosis, continues as long as calcium and absorbable alkali are ingested.[3] To the extent that volume contraction supervenes at any point due to vomiting, diuretics, or the natriuretic effects of hypercalcemia, the hypercalcemia and alkalosis will be intensified. The severely hypercalcemic patient may present with acute toxicity.

MANAGEMENT STRATEGIES

Withdrawing the calcium and absorbable alkali improves the clinical situation and usually resolves the milk-alkali syndrome rapidly. Isotonic saline and furosemide are effective in treating hypercalcemia and metabolic alkalosis and may be prescribed for symptomatic patients. Soon after hydration therapy is initiated, hypocalcemia may occur, and its correction may be slow due to chronic suppression of the parathyroid, which cannot respond immediately to the rapid lowering of serum calcium.[4] As a part of milk-alkali syndrome, hypercalcemia rarely causes pancreatitis, though it's possible.[5]

Table. Initial laboratory study results

Laboratory study	Patient's values	Normal values
Serum sodium	122 mEq/L	136–145 mEq/L
Blood urea nitrogen	49.1 mg/dL	7–18 mg/dL
Serum bicarbonate	28.8 mEq/L	22–29 mEq/L
Serum creatinine	5.3 mg/dL	0.6–1.3 mg/dL
Serum magnesium	2.7 mg/dL	1.8–2.4 mg/dL
Serum calcitriol (1,25-dihydroxycholecalciferol)	26.7 pg/mL	15.9–55.6 pg/mL
Thyroid stimulating hormone	2.77 mIU/mL	0.34–4.82 mIU/mL
24-hour urinary calcium excretion	1.7 mg/day	100–250 mg/day
Parathyroid hormone-related peptide	< 0.3 pmol/L	0.0–1.5 pmol/L
Intact parathyroid hormone	8 pg/mL	10–65 pg/mL

Despite the resurgence of milk-alkali syndrome,[2,6] physicians often fail to consider this condition in patients with hypercalcemia. This may be due in part to the fact that patients, not considering calcium carbonate a medication, tend not to volunteer the fact that they are using large amounts, and physicians fail to ask patients with hypercalcemia whether they are using antacids or taking calcium supplements.

In light of the current emphasis on the importance of calcium in treating and preventing osteoporosis, it's critical for clinicians to incorporate questions about calcium supplements and antacids into the medical history survey. Individuals with mild renal insufficiency, volume contraction, and those being treated with a thiazide diuretic (which directly reduces calcium excretion) are at elevated risk for milk-alkali syndrome and, when patients take calcium concurrently with vitamin D, their risk is even greater than when they take calcium alone. ●

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CORRECTION

Due to a typographical error on CME test 86 and CE test 89—which appeared on pages 100 and 102, respectively, of the April 2004 issue and pertained to the article "Occupational Eye Accidents—Assessing Risk Among Hospital Workers"—there is no correct answer for question number 6. Therefore, *Federal Practitioner's* CME and CE providers have agreed to award credit to any tests that failed on the basis of this question. If you failed one of these tests and believe you may be entitled to credit, please contact Albert Einstein College of Medicine Office of CME by calling (718) 920-6674 or faxing (718) 798-2336 or Mercer University Southern School of Pharmacy CE Office by calling (678) 547-6174 or faxing (678) 547-6364. Please be sure to include *"Federal Practitioner* CME test 86" or *"Federal Practitioner* CE test 89" in your inquiry. Our thanks to the astute reader who pointed out this error.

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