MILK-ALKALI SYNDROME INDUCED BY 1,25(OH)2D IN A PATIENT WITH HYPOPARATHYROIDISM

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Milk-alkali syndrome was first described 70 years ago in the context of the treatment of peptic ulcer disease with large amounts of calcium and alkali. Although with current ulcer therapy (H-2 blockers, omeprazole, and sucralfate), the frequency of milk-alkali syndrome has decreased significantly, the classic triad of hypercalcemia, alkalosis, and renal impairment remains the hallmark of the syndrome. Milk-alkali syndrome can present serious and occasionally life-threatening illness unless diagnosed and treated appropriately. This article presents a patient with hypoparathyroidism who was treated with calcium carbonate and calcitriol resulting in two admissions to the hospital for milk-alkali syndrome. The patient was successfully treated with intravenous pamidronate on his first admission and with hydrocortisone on the second. This illustrates intravenous pamidronate as a valuable therapeutic tool when milk-alkali syndrome presents as hypercalcemic emergency. (*J Natl Med Assoc.* 1996;88:313-314.)

Key words • milk-alkali syndrome
• hypoparathyroidism

Classical milk-alkali syndrome presents with a triad of hypercalcemia, alkalosis, and renal impairment.[1] Milk-alkali syndrome was first described in 1923 in patients with peptic ulcer disease ingesting large amounts of calcium and absorbable alkali.[2] Milk-alkali syndrome is rarely seen today because of the advent of modern ulcer therapy with nonabsorbable antacids, histamine-2 blockers, omeprazole, and sucralfate. This article presents a patient with hypoparathyroidism who was treated with calcium carbonate and calcitriol resulting in two hospital admissions for milk-alkali syndrome.

CASE REPORT

A 66-year-old female with mild renal insufficiency, gout, peptic ulcer disease, hypothyroidism, and hypoparathyroidism secondary to thyroidectomy for benign reasons presented complaining of nocturia, polyuria, nausea, and watery diarrhea of 2 weeks duration, and confusion and unsteadiness for 1 week. The patient reported a one-pint milk intake per week. For the past 4 months, she was taking calcium carbonate 1500 mg/day and calcitriol 1 μg/day for hypoparathyroidism. Her other medications included cimetidine (400 mg/day), allopurinol (100 mg/day), and levothyroxine (0.1 mg/day).

On examination, she was lethargic and dehydrated, with a pulse of 68 beats/minute and blood pressure of 118/52 mm Hg. Other pertinent findings were drowsiness, proximal muscle weakness, and epigastric tenderness. Laboratory data on admission were as follows: serum calcium, 17.0 mg/dL (normal range: 8.7 to 10.7); ionized calcium, 8.37 mg/dL (4.6 to 5.3); serum phosphorus, 4.2 mg/dL (2.6 to 4.9); chloride, 89 mg/dL (98 to 110); blood urea nitrogen, 47 mg/dL (5 to 25); creatinine, 5.3 mg/dL (0.5 to 1.4); serum bicarbonate, 40 mmol/L (24 to 31); arterial blood pH, 7.48; urine pH, 8;

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thyrotropin, 1.4 μU/mL (0.3 to 5); parathyroid hormone <1 pg/mL (10 to 65); 25(OH)D, 69 ng/mL (9 to 52); and 1,25(OH)2D, 59 pg/mL (15 to 60). Urine and serum immunoelectrophoresis results were normal, and a 24-hour urine collection for calcium was 402 mg (150 to 300). Mammogram and renal ultrasound were normal. Renal flow scan revealed moderate decrease in blood flow and function in a symmetric pattern. A roentgenogram of the abdomen showed no renal stones and no interstitial calcifications.

Initial treatment with intravenous saline and loop diuretics resulted in a mild decrease in the serum calcium. Therefore, therapy with intravenous pamidronate (aminohydroxypropylidene diphosphonate) of 60 mg was initiated. Forty eight hours later, the serum calcium was normal (10.4 mg/dL), and renal functions had improved. During the next week, serum calcium dropped to 7.1 mg/dL and serum phosphorus rose to 5.6 mg/dL. The patient was restarted on calcium carbonate 3000 mg/day and calcitriol 0.5 μg/day. Five days later, she was discharged from the hospital on a regimen of calcium carbonate 1500 mg/day and calcitriol 0.5 μg/day. On the day of discharge, the serum calcium was 7.9 mg/dL, creatinine was 2.4 mg/dL, and blood urea nitrogen was 33 mg/dL.

The patient was readmitted a month later because of nausea, vomiting, anorexia, and weakness of 2 days duration. Except for trace pitting edema in both legs, the results of the rest of the physical examination were unremarkable. Laboratory tests revealed the following values: serum calcium, 15.2 mg/dL; phosphorus, 3.5 mg/dL; blood urea nitrogen, 42 mg/dL; creatinine, 4.4 mg/dL; bicarbonate, 34 mmol/L; arterial blood pH, 7.44; and urine pH, 7. On further review of her history, the patient stated that she had been drinking one pint of milk daily and ingesting calcium carbonate tablets 1500 mg/day and calcitriol 0.5 μg/day. The patient received intravenous saline and intravenous hydrocortisone 300 mg/day, which resulted in normalization of serum calcium level within 48 hours. Two days later, she was discharged on a regimen of calcium carbonate 1500 mg/day and calcitriol 0.25 μg/day. On the day of discharge, her serum calcium was 9.6 mg/dL, creatinine was 2.1 mg/dL, and blood urea nitrogen was 24 mg/dL.

DISCUSSION

This patient presented with classical features of milk-alkali syndrome: hypercalcemia, alkalosis, and renal failure. In addition, hypercalciuria and elevated levels of 25(OH)D and 1,25(OH)2D were present. In view of undetectable parathyroid hormone levels, high-normal phosphorus, and renal failure, the renal 1-hydroxylation of 25(OH)D into 1,25(OH)2D would be inhibited. Therefore, the oral intake of borderline-high dose calcitriol in the presence of renal insufficiency accounts for high levels of 1,25(OH)2D. This in turn increased gastrointestinal fractional absorption of calcium carbonate leading to hypercalcemia, alkalosis,[3] and renal impairment.[4] Finally, dehydration caused by vomiting, diarrhea, and polyuria in this clinical setting further impaired renal function.

In addition to intravenous saline, the patient received treatment with pamidronate and hydrocortisone. Both therapies were equally effective in lowering the serum calcium level.

CONCLUSION

Unlike the "classical" milk-alkali syndrome in which both serum parathyroid hormone and 1,25(OH)2D levels are low,[5] the patient described here had an elevated 1,25(OH)2D level in a face of undetectable parathyroid level. When milk-alkali syndrome presents as a hypercalcemic emergency, intravenous pamidronate can be a valuable therapeutic tool.

Literature Cited

1. Orwoll ES. The milk alkali syndrome: current concepts. *Ann Intern Med.* 1982;97:242-248.

2. Hardt LL, Rivers AB. Toxic manifestations following the alkaline treatment of peptic ulcer. *Arch Intern Med.* 1923;31:171-180.

3. McMillan DE, Freeman RB. The milk alkali syndrome: a study of the acute disorder with comments on the development of the chronic condition. *Medicine (Baltimore).* 1965;44:485-501.

4. Human HD, Ichikawa I, Troy JL, Brenner BM. Evidence for a parathyroid hormone-dependent influence of calcium on the glomerular ultrafiltration coefficient. *J Clin Invest.* 1978;61:32-40.

5. Abreo K, Aklakha A, Kilpatrick S, Flanagan R, Webb R, Shakamuri S. The milk-alkali syndrome: a reversible form of acute renal failure. *Arch Intern Med.* 1993;153:1005-1010.