Hypercalcemia and acute renal failure associated with calcium carbonate consumption in a patient with hypoparathyroidism

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Milk-alkali syndrome was first recognized in the 1920s during administration of the popular "Sippy" regimen for peptic ulcer disease, consisting of large amounts of milk and sodium bicarbonate. Toxic reactions associated with alkalosis and renal insufficiency were noted shortly thereafter, but the plasma calcium concentration was not measured [1]. In 1936, a report that associated hypercalcemia with the alkalosis and renal failure in patients treated with the "Sippy" regimen was published [2]. This syndrome is rarely seen today in this group of patients because of the replacement of the older peptic ulcer treatment with new agents, but it is now increasingly prevalent in patients (mostly middle-aged women) who use drugs containing calcium carbonate for the prevention or the treatment of osteoporosis [3]. So, it was recommended that the term 'milk-alkali syndrome' should be replaced by the term 'calcium-alkali syndrome', since the older term no longer reflects the etiologic origin [4].

A 60-year-old woman visited our hospital with a 1-week history of nausea, vomiting, anorexia and general weakness. Her past medical history included a total thyroidectomy 20 years ago for multinodular goiter, diabetes mellitus, hypertension, dyslipidemia and chronic renal failure (creatinine 115 µmol/l, estimated glomerular filtration rate (eGFR) 52 ml/min). She was taking levothyroxine (0.1 mg/day) for iatrogenic hypothyroidism, calcium carbonate (1000 mg/day) and alfacalcidol (1 µg/day) for iatrogenic hypoparathyroidism [5]. Her other medications included vildagliptin (100 mg/day), metformin (2000 mg/day), gliclazide (30 mg/day), quinapril (20 mg/day), atorvastatin (20 mg/day), folic acid (5 mg/day) and hydroxocobalamin (1 mg/month *i.m.*). On examination she was dehydrated with a pulse of 96 beats/min and blood pressure of 130/75 mm Hg. Laboratory data on admission were as follows (Table I): glucose 4.8 mmol/l (reference range (RR): 3.9 to 6.9 mmol/l), creatinine 301 µmol/l (RR: 53–106 µmol/l), urea 22.31 mmol/l (RR: 1.83–8.99 mmol/l), serum calcium 3.67 mmol/l (RR: 2.05–2.64 mmol/l), urinary calcium 9.16 mmol/l, serum phosphate 0.77 mmol/l (RR: 0.81–1.61 mmol/l), chloride 94 mmol/l (RR: 98–110 mmol/l), magnesium 0.63 mmol/l (RR: 0.65–1.05 mmol/l), potassium 5.8 mmol/l (RR: 3.5–5.3 mmol/l), sodium 137 mmol/l (RR: 135–145 mmol/l), albumin 46 g/l (RR: 34–50 g/l), alkaline phosphatase 43 IU/l, arterial blood pH 7.46, serum bicarbonate 29 mmol/l, parathyroid hormone (PTH) < 1 ng/l (RR: 12–88 ng/l), 25(OH)D 100 nmol/l (RR: 47–145 nmol/l), $1,25(OH)_2D_3$ 99 pmol/l (RR: 62–192 pmol/l) (Table I).

Table I. Laboratory data

Serum laboratory data	On admission	48 hours later	1 year later
Creatinine [µmol/l]	301	177	115
Urea [mmol/l]	22.31	21.4	20.7
Calcium [mmol/l]	3.67	2.47	2.42
Albumin [g/l]	46	40	43
Bicarbonate [mmol/l]	29	28	22
Sodium [mmol/l]	137	142	141
Potassium [mmol/l]	5.8	5.2	5.2
Magnesium [mmol/l]	0.63	0.51	0.57
Phosphate [mmol/l]	0.77	0.97	1.55
PTH [ng/l]	< 1		8

PTH – parathyroid hormone

Urinalysis and serum immunoelectrophoresis results were within the RR and renal ultrasound was normal. Mammography screening, computed tomography (CT) scan of thorax and abdomen, gastroscopy and colonoscopy were negative for malignancy.

Treatment with intravenous saline (NaCl 0.9%) and withdrawal of calcium carbonate and vitamin D resulted in a progressive decrease in the serum calcium. Forty-eight hours later nausea and other symptoms improved, serum calcium level was normal (2.47 mmol/l) and renal function had improved (serum creatinine 177 µmol/l). The patient was discharged from the hospital 1 week later, treated with low doses of vitamin D and calcium carbonate, while she was on close monitoring and adjustment of treatment. One year later the patient's hypoparathyroidism is being treated with 1000 mg/day calcium carbonate and 0.5 µg/day alfacalcidol. The level of serum calcium is 2.42 mmol/l, and the serum creatinine level is 115 µmol/l.

The patient presented with the classical features of milk-alkali syndrome: hypercalcemia, metabolic alkalosis and impaired renal function associated with ingestion of calcium and alkali. The clinical presentation of this syndrome may vary depending on the severity of hypercalcemia. The patient may be asymptomatic or may present with nausea, vomiting and weakness, as was the case in our patient, and changes in mental status if hypercalcemia is severe.

The pathophysiology of milk-alkali syndrome is poorly understood, but it has been suggested that some individuals seem to absorb more calcium than others [6, 7]. It is possible that some patients may not adequately suppress calcitriol production in response to a large amount of calcium, resulting in hyperabsorption of calcium and hypercalcemia. Hypercalcemia is the major cause of the subsequent metabolic derangements, including metabolic alkalosis and acute renal failure, since it causes renal vasoconstriction, thereby reducing the GFR and calcium excretion. Hypercalcemia also increases sodium excretion and induces depletion of total body water due to polyuria leading to hypovolemia and prerenal azotemia, which is evident in our case due to the increase of the ratio of urea/creatinine (almost 40/1 in our patient) [8]. The phosphorus-binding properties of the calcium carbonate lead to hypophosphatemia, which in turn stimulates the renal metabolism of calcitriol. Further, calcitriol increases the absorption of calcium by the gut. The levels of calcitriol in this syndrome are generally low due to hypercalcemia, although in some cases they are normal or rarely increased [9]. The hypovolemia and the decreased GFR lead to a further increase in the amount of calcium in plasma. Increased renal tubular bicarbonate reabsorption due to volume depletion, ingestion of an alkali and the suppression of parathyroid hormone (PTH), in response to hypercalcemia, can produce and maintain metabolic alkalosis [4]. Several factors can contribute to the development of the syndrome, such as old age, preexisting renal failure (which was known in our patient), the volume depletion and medication that can reduce the GFR, such as angiotensin-converting inhibitors (our patient was treated with quinapril) and nonsteroidal anti-inflammatory drugs [6]. Thiazide use is also a contributing factor by increasing renal calcium absorption and by causing volume depletion. Pregnant women may also be at increased risk, due to increased calcitriol levels and increased calcium absorption [10].

Withdrawal of the offending agent and intravenous volume expansion usually are enough to reverse hypercalcemia, alkalosis and renal insuf-

ficiency. Hemodialysis may be required in rare cases.

Milk-alkali syndrome is characterized by the classic triad of hypercalcemia, metabolic alkalosis and renal failure, associated with ingestion of calcium and alkali. The pathophysiology of this syndrome is poorly understood, but it has been suggested that some individuals seem to absorb more calcium than others. Withdrawal of the offending agent and intravenous volume expansion usually are enough for the treatment of milk-alkali syndrome.

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