

In-Depth Clinical Review

Hypercalcemic crisis induced by calcium carbonate

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Abstract

We report a rare case of drug-induced hypercalcemic crisis in an elderly male resulting from calcium-containing supplements facilitated by thiazide diuretic and angiotensin-converting enzyme inhibitor. A 61-year-old male presented with hypercalcemic crisis along with renal insufficiency and metabolic alkalosis, mimicking the 'calcium-alkali syndrome'. The patient responded to aggressive intravenous hydration along with emergent hemodialysis and salmon calcitonin. He did not have hyperparathyroidism or malignancy. History revealed an average daily intake of only 1200 mg of calcium carbonate along with vitamin D 1000 U/day over an extended period of time. The patient completely recovered in 3 days and had normal serum calcium, parathyroid hormone and phosphorous level at 3-month follow-up. The case highlights the life-threatening perils of indiscriminate and often excessive intake of calcium-containing supplements in an appropriate clinical setting. We also briefly discuss the epidemiology, clinical and laboratory features along with the recent advances in the understanding of the pathophysiology of calcium-alkali syndrome.

Keywords: calcium-alkali syndrome; hypercalcemic crisis; milk-alkali syndrome

History and background

Hypercalcemic crisis is a rare life-threatening condition secondary to decompensated hypercalcemia leading to renal failure and altered mental status. The majority of cases are caused by primary hyperparathyroidism [1]. Severe hypercalcemia is known to occur when the corrected serum calcium is above 15 mg/dL (3.74 mmol/L), which may be accompanied by symptoms of intractable nausea, vomiting and constipation, somnolence and coma, electrocardiographic (ECG) finding of shortened QTc interval as well as sudden cardiac arrest. Although hyperparathyroidism and hypercalcemia of malignancy are more prevalent, hypercalcemia resulting from increased consumption of calcium and vitamin D supplements as part of the 'milk-alkali syndrome' is the third most common cause of hospital admission for hypercalcemia [2–5].

Historically, milk-alkali syndrome had been described predominantly in men as a toxic side effect resulting from intensive treatment of peptic ulcer disease (PUD) with calcium-containing antacids and milk in the early twentieth century [6]. Prevalence of the condition declined following the introduction of histamine blockers and proton-pump inhibitors for the treatment of PUD, and in recent years the syndrome has been primarily reported in older individuals receiving treatment for osteoporosis [2, 3, 5, 6]. As the name no longer indicates the etiology of the disorder, milk-alkali syndrome has been renamed 'calcium-alkali syndrome' [4]. We report a

rare case of hypercalcemic crisis in an elderly male resulting from ingestion of calcium supplements mimicking the calcium-alkali syndrome [4].

Case

Clinical history and initial laboratory data

A 61-year-old white male presented to the emergency room with a history of increased confusion for 3 days. His past medical history was significant for type 2 diabetes mellitus, hypertension, hyperlipidemia, depression, restless leg syndrome, cluster headaches, benign prostatic hypertrophy and kidney stones. There was no family history of kidney stone disease, hyperparathyroidism or hypercalcemia. Blood pressure was 157/82 mmHg, pulse 108 b.p.m. and oxygen saturation was 94% on room air. Physical examination was remarkable only for dryness of oral mucosa and the confusion. His medications included desipramine 75 mg/day, lisinopril 10 mg/day, diltiazem CD 240 mg/day, metformin 500 mg two times daily, hydrochlorothiazide 25 mg daily, lovastatin 40 mg daily, glipizide XL 2.5 mg daily, divalproex sodium (Depakote; Abbott Laboratories, Abbott Park, IL, USA) 500 mg four times daily, sitagliptin (Januvia; Merck & Co., Whitehouse Station, NJ, USA) 100 mg daily, pramipexole (Mirapex; Boehringer Ingelheim GmbH, Ingelheim, Germany) 0.25 mg daily, zolpidem 10 mg/day, bupropion (Wellbutrin; Valeant Pharmaceutical International, Inc., Mississauga,

Ontario, Canada) 300 mg daily, alfuzosin (Uroxatral; Sanofi-aventis, Bridgewater, NJ, USA) 10 mg daily, Tums ultra 3–4 tablets daily (calcium carbonate 1000 mg/tablet, equivalent to 400 mg of elemental calcium/tablet) and vitamin D3 1000 U daily. He denied a history of excessive milk consumption.

The initial biochemical profile revealed profound hypercalcemia [serum total calcium 22.3 mg/dL (5.58 mmol/L) and ionized calcium markedly elevated at 9.1 mg/dL (2.28 mmol/L)] (Table 1). The parathyroid hormone (PTH)-related peptide was 7 pg/mL (normal reference interval 14–27 pg/mL). He had normal liver function test, coagulation profile, thyroid function tests and hematocrit. Serum vitamin A or retinol was 37 µg/dL (normal reference interval 38–106). Multiple myeloma was ruled out based on normal serum and urine immunofixation studies. Examination of urine revealed 2+ protein, trace amount of blood, 0–3 red blood cells/high-power field, 0–4 white blood cells/high-power field, but no cellular or granular casts. Twenty-four-hour urine calcium was elevated at 454 mg (normal 100–300).

ECG showed sinus tachycardia and non-specific ST-T wave changes with normal corrected QT interval. A contrast computerized axial tomography (CT) scan of the brain, thorax, abdomen and pelvis revealed no evidence of stroke, extensive coronary calcification, punctate non-obstructing stone in mid-right and lower parts of the right kidney without hydronephrosis, calcification in the aorta, and central and peripheral prostate calcification.

Treatment and follow-up

The patient received aggressive intravenous hydration with isotonic fluids, furosemide 40 mg intravenous, two doses of salmon calcitonin 400 U subcutaneously at 6 h interval, in addition to a single session of emergent hemodialysis with low calcium bath. Over the next 48 h, there was a gradual drop in the serum calcium level while only on continuous hydration with isotonic fluid. A week later, his serum calcium, serum creatinine and bicarbonate values were normal, while a repeat PTH level was 40 pg/mL (40 ng/L). Given the severe hypercalcemia with concomitantly normal serum phosphorous, appropriately suppressed PTH, normal PTHrP and normal serum 25(OH)D, the likelihood of hypercalcemic crisis precipitated by over-ingestion of calcium carbonate was suspected.

Follow-up studies undertaken 2.5 months later revealed angiotensin-converting enzyme 7 U/L (normal reference

interval 9–67), normal values of serum creatinine, serum calcium, 24 h urine calcium and protein, serum 25(OH)D and PTH levels. The serum 1,25-dihydroxyvitamin D [1,25(OH)₂D] was 23 pg/mL (normal reference interval 18–72 pg/mL). There was no clinical or biochemical evidence of malignancy 3 months after the initial presentation of hypercalcemia.

Epidemiology

The majority of cases of calcium-alkali syndrome are observed in middle-aged women with a history of excessive intake of calcium carbonate either for dyspepsia and/or treatment of osteoporosis. In the case of male patients, milk-alkali syndrome resulted predominantly from the consumption of calcium carbonate-containing antacids [2, 3, 6]. Most of these male patients had an underlying history of reflux esophagitis and dyspepsia while few had hypertension with exposure to diuretics and/or angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs). The notable features in our case are the severity of hypercalcemia, in an elderly male patient, secondary to an indiscriminate intake of calcium supplements, and this constellation is more aptly rendered calcium-alkali syndrome [4]. The 1,25(OH)₂D preparations are prescription medications and the patient was not taking any of those preparations. The normal serum concentration of 25(OH)D rules out vitamin D overdose. Hypercalcemia of malignancy was ruled out, given the normal study results of CT scan, normal serum and urine immunofixation studies and normal PTH-related peptide level. Moreover, the serial serum calcium level remained normal 4 months after the initial presentation, thus precluding malignancy as an etiology of initial hypercalcemia. As malignancy, sarcoidosis, vitamin D overdose and primary hyperparathyroidism were ruled out, an excessive intake of calcium supplements (Tums Ultra) as the cause of hypercalcemia was considered. The patient was taking at least 3–4 tablets of Tums ultra (1200–1600 mg elemental calcium/day) along with a vitamin D supplement (1000 U/day).

Clinical and laboratory features

The classic triad of milk-alkali syndrome consists of hypercalcemia and varying degrees of renal failure and metabolic alkalosis resulting from the ingestion of large amounts of calcium and absorbable alkali [2, 5]. The clinical presentation may have a wide spectrum depending upon the severity of hypercalcemia. The patient may be relatively asymptomatic, being only dehydrated or may present with symptoms of intractable nausea, vomiting and constipation, and altered mental status, all resulting from severe hypercalcemia. The renal insufficiency can vary in severity even in cases of severe hypercalcemia. For example, Picolos *et al.* reported three patients with severe hypercalcemia, as high as 22.70 mg/dL (5.65 mmol/L) in one case, whose average serum creatinine was 1.4 mg/dL (123.8 micromol/L). The severity of metabolic alkalosis is similarly a variant, induced and maintained by gastrointestinal alkali absorption, increased renal tubular bicarbonate reabsorption from volume depletion induced by diuretic exposure (as in our case), compounded by accompanying renal insufficiency and suppression of

Table 1. Laboratory characteristics during follow-up

Laboratory values	Day 1	Day 2	Day 3	Day 7	Week 10	Month 4
Serum calcium (mg/dL)	22.3	13.7	12.8	8.3	9.6	9.0
Serum phosphorus (mg/dL)	4.5			4.0		
BUN (mg/dL)	33	32	34	16	26	28
Serum creatinine (mg/dL)	1.55	1.40	1.36	0.74	0.94	1.0
Serum bicarbonate (mEq/L)	30	28		27	30	28
Serum magnesium (mg/dL)	1.4			1.9		
Intact PTH (pg/mL) ^a	6			40	13	30
25(OH)D (ng/mL) ^b	53				49	36
24 h urine Ca (mg) (normal range 100–300 mg)	454				79	

^aPTH: normal reference interval 10–65 pg/mL.

^b25(OH)D: normal reference interval 30–100 ng/mL.

parathyroid hormone in response to hypercalcemia [7]. Also, the ingestion of calcium carbonate does not provide nearly as much absorbable base as sodium bicarbonate (probably due the 'dissociation' constant of Ca^{2+} salts) and perhaps less than the magnesium and bismuth salts used in the past accounting for a historical classic variety of milk-alkali syndrome. In fact, both Picolos *et al.*'s and Beall and Scofield's retrospective studies revealed an average serum bicarbonate level of 30 mmol/L, while 6 patients out of 11 in Picolos *et al.*'s study were reportedly taking diuretics (3 loop diuretics, 1 hydrochlorothiazide and 2 both loop and thiazide-like diuretic). The renal insufficiency and metabolic alkalosis seemed mild and transient in our patient and most likely responded well to aggressive hydration. Most cases of milk-alkali syndrome have elevated serum phosphorous which was not seen in our patient. We postulate that in cases of calcium supplement overdose, low-to-normal levels of serum phosphorus are expected due to increase binding by calcium carbonate present in most calcium supplement preparations [4, 5].

Pathophysiology

The calcium homeostasis is maintained by the interplay between bone turnover, intestine absorption and renal reabsorption, governed by PTH, $1,25(\text{OH})_2\text{D}$, ionized calcium and their respective receptors. The bone serves as the predominant repository of calcium in the body, and hence, the relative rates of bone formation and resorption influence calcium balance [8]. With advancing age, there is a negative bone balance characterized by greater bone resorption than formation, resulting in age-related bone loss. This age-related physiological change renders one more vulnerable to increased serum calcium due to superfluous ingestion of calcium and alkali supplements [6]. In addition, for the prevention of osteoporosis, most elderly subjects consume exceedingly large quantities of calcium supplements [4, 9]. The intestinal calcium absorption depends on factors like dietary intake, gastric acidity and $1,25(\text{OH})_2\text{D}$. In general, at normal calcium intake, $1,25(\text{OH})_2\text{D}$ -dependent calcium transport accounts for the majority of absorption, whereas passive calcium absorption accounts for an average of 15% of overall calcium absorption [10]. This passive pathway however becomes the major conduit for calcium absorption when excessive amounts of calcium supplements are consumed [11], which conceivably occurred in our patient. Prior to the hypercalcemic crisis, he was, on average, taking 3–4 tablets of Tums Ultra (elemental calcium of 400 mg/tablet) on a conservative estimate. A detailed history also revealed that he often indulged in an excess of over 4–6 tablets/day on and off to treat his heartburn. Further, the findings of excessive metastatic calcification from the CT scan may be an indirect clue towards excessive calcium load over the past several years. Even though doses exceeding >4 g/day of elemental calcium are known to generate calcium-alkali syndrome, there are case reports that an intake of 1.0–1.5 g/day of elemental calcium can do the same [2, 5]. Picolos *et al.* reported eight patients taking 2000 mg or less of elemental calcium/day for an unspecified period when diagnosed with milk-alkali syndrome. Out of these eight patients, six had severe hypercalcemia (serum calcium >15 mg/dL), three of whom were taking diuretics, while

additional two patients were taking calcitriol (1,25-hydroxy vitamin D).

Hypercalcemia directly causes renal vasoconstriction, which results in decreased glomerular filtration rate (GFR), thereby decreasing the amount of filtered calcium [5]. In our patient, this was further compounded by thiazide diuretic which through volume depletion would promote metabolic alkalosis as well as enhanced proximal tubular calcium reabsorption. Moreover, the intake of the ACE-I lisinopril would have further reduced net calcium excretion through a reduction in GFR.

Recent literature underscores the integrative role of calcium-sensing receptors (CaSRs) and the calcium selective channel called transport transient receptor potential vanilloid membrane 5 (TRPV5) in sustaining the syndrome [4] (Figure 1). The sensitivity of the receptor and the activity of the channel are increased by hypercalcemia at the thick ascending loop of Henle (TAH), distal convoluted tubule (DCT) and the collecting duct (CD). CaSR at the TAH is located primarily on the basolateral cell membrane. Activated by high serum calcium concentrations, this inhibits the renal outer medullary kidney (ROM-K) channel located on the apical membrane, which blunts the activity of the Na-K-Cl-Cl co-transporter (NKCC) stationed on the apical membrane [12]. The activated CaSR can also directly inhibit NKCC activity. This results in a loop diuretic-like effect of decreased sodium and calcium absorption as well as a reduction in kidney's concentrating ability, both of which lead to increased urinary

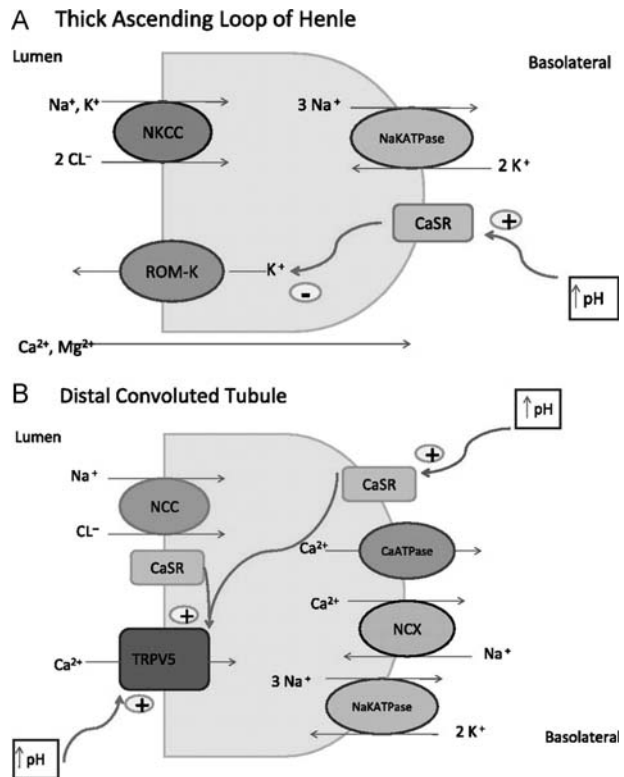


Fig. 1. Mechanisms for renal calcium transport depend on the location of the CaSR and TRPV5 channel. (A) Thick ascending loop of Henle. (B) Distal convoluted tubule. NKCC, sodium potassium-2-chloride co-transporter; ROM-K, renal outer medullary potassium channel; NaKATPase, sodium-potassium ATPase; +, stimulates; -, inhibits; NCC, sodium chloride co-transporter; NCX, sodium-calcium exchanger. (Reproduced with permission from Patel and Goldfarb [4].)

Table 2. Calcium-alkali syndrome

Cause	Mostly intake of calcium carbonate supplements (1–1.5 g of elemental calcium/day) with or without vitamin D analogues, like ergocalciferol or calcitriol (2, 3), rarely antacids like magnesium oxide (2, 5)
Gender	Mostly females, post-menopausal, pregnant or bulimic (4)
Co-morbid condition	Rare reported cases of middle to elderly aged males Gastritis, dyspepsia Osteoporosis Chronic kidney disease, hypertension Diuretic therapy, few cases with ACE-Is or ARBs
Lab findings	Hypercalcemia, often severe Varying degree of renal insufficiency and metabolic alkalosis Normal or low normal serum phosphorus

calcium delivery to the DCT and CD. At the DCT, high urine calcium activates apical CaSR which in turn increases the calcium reabsorption via TRPV5 channels [13]. Finally, in the CD, activated CaSR (mediated via high urine calcium) on the apical membrane causes (i) reduced expression of aquaporin 2 water channels, thereby reducing water reabsorption and excreting more dilute urine [14] and (ii) stimulation of proton secretion via H-ATPase receptor [15]. The aftermath of these two effects, namely increased dilution and acidification of the urine, may explain lower incidence of calcium salts precipitation and stone formation in the tubules described in this syndrome. Moreover, the above-mentioned renal CaSR and TRPV5 effects are enhanced by systemic metabolic alkalosis through increased sensitivity of the receptor and the activity of the channel [16].

In summary, the cascade of actions at the receptors and channels all along the renal tubule serves to induce volume depletion and enhanced tubular reabsorption of calcium and bicarbonate.

Management and conclusion

Hypercalcemia crisis due to calcium carbonate ingestion should mandate an extensive workup to rule out the hyperparathyroid disease state, occult malignancy and sarcoidosis while prompting a detailed history and review of medications and laboratory findings (namely even mild renal insufficiency and metabolic alkalosis) for a more definitive diagnosis of calcium-alkali syndrome. Initial management would involve one session of emergent hemodialysis to reduce the markedly elevated serum calcium in a symptomatic patient with or without ECG changes, aggressive hydration with isotonic fluid and induced diuresis with or without salmon calcitonin or bisphosphonates. It is recommended to have close serial follow-up for the patient to rule out any evidence of occult malignancy for next 6 months.

While highlighting the changing epidemiology and characteristics of erstwhile milk-alkali syndrome, now more appropriately called calcium-alkali syndrome

(Table 2), the syndrome does not occur in all people who ingest large amounts of calcium and alkali supplements. Alternatively, a daily intake of <2000 mg of elemental calcium may generate the syndrome through the concomitant risk factors like elderly age, renal insufficiency, altered endocrine and intestinal function, bone metabolism and the low volume status.

Conflict of interest statement. None declared.

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