Milk-alkali syndrome: a 'quick ease' or a 'long-lasting problem'

Mawson Wang[1], Catherine Cho[1], Callum Gray[1], Thora Y Chai[2,3], Ruhaida Daud[1] and Matthew Luttrell[2]

[1]Nepean Blue Mountains Local Health District, Katoomba, New South Wales, Australia, [2]Department of Endocrinology, Nepean Blue Mountains Local Health District, Kingswood, New South Wales, Australia, and [3]Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

Correspondence should be addressed to M Luttrell
Email
luttrell.matthew@gmail.com

Summary

We report the case of a 65-year-old female who presented with symptomatic hypercalcaemia (corrected calcium of 4.57 mmol/L) with confusion, myalgias and abdominal discomfort. She had a concomitant metabolic alkalosis (pH 7.46, HCO_3^- 40 mmol/L, pCO_2 54.6 mmHg). A history of significant Quick-Eze use (a calcium carbonate based antacid) for abdominal discomfort, for 2 weeks prior to presentation, suggested a diagnosis of milk-alkali syndrome (MAS). Further investigations did not demonstrate malignancy or primary hyperparathyroidism. Following management with i.v. fluid rehydration and a single dose of i.v. bisphosphonate, she developed symptomatic hypocalcaemia requiring oral and parenteral calcium replacement. She was discharged from the hospital with stable biochemistry on follow-up. This case demonstrates the importance of a detailed history in the diagnosis of severe hypercalcaemia, with MAS representing the third most common cause of hypercalcaemia. We discuss its pathophysiology and clinical importance, which can often present with severe hypercalcaemia that can respond precipitously to calcium-lowering therapy.

Learning points:

- Milk-alkali syndrome is an often unrecognised cause for hypercalcaemia, but is the third most common cause of admission for hypercalcaemia.
- Calcium ingestion leading to MAS can occur at intakes as low as 1.0–1.5 g per day in those with risk factors.
- Early recognition of this syndrome can avoid the use of calcium-lowering therapy such as bisphosphonates which can precipitate hypocalcaemia.

Background

Milk-alkali syndrome (MAS) is characterised by the triad of hypercalcaemia, renal impairment and metabolic alkalosis due to the consumption of calcium and absorbable alkali. First described at the turn of the twentieth century, when milk and alkali were commonly prescribed for peptic ulcer disease, MAS has become less frequent in modern society with the advent of proton pump inhibitors and histamine-2 receptor antagonists (1). However, recent decades have seen a resurgence in MAS due to increased consumption of over-the-counter calcium supplementation by postmenopausal women, transplant recipients and dialysis patients (1). Pregnant women are also at risk due to volume depletion and metabolic alkalosis caused by hyperemesis and physiological upregulation of intestinal calcium absorption (2). We report a case of a postmenopausal female who presented with symptomatic hypercalcaemia after ingestion of large quantities of calcium carbonate-containing antacid.

Case presentation

A 65-year-old female presented to the emergency department with a 2-week history of generalised lethargy, anorexia, vomiting, abdominal discomfort, constipation, myalgias and altered mental state. There were no constitutional symptoms of fevers, night sweats or unintentional weight loss. Her background was significant for localised cervical cancer treated with radiotherapy over 10 years ago. She reported no regular prescription medications; however, she was subsequently admitted to ingesting up to 12 tablets of the antacid Quick-Eze (calcium carbonate, magnesium carbonate and magnesium trisilicate), equivalent of 3.6 g elemental calcium daily for 1 week to help alleviate reflux symptoms. On examination, she was haemodynamically stable. Neurological examination was grossly intact although limited by acute delirium. She exhibited dry mucous membranes and otherwise had an unremarkable cardiorespiratory and gastrointestinal examination. She had marked diffuse tenderness to palpation over her shoulders and hip girdle.

Investigation

Investigations on admission (Table 1) identified a severe hypercalcaemia (corrected calcium: 4.57 mmol/L (2.15–2.55)), acute kidney injury (creatinine: 171 μmol/L (45–90), urea: 15.3 mmol/L (3.5–8.0) and estimated glomerular filtration rate: 27 mL/min/1.72 m² (≥90)), hyponatraemia: 129 mmol/L (135–145), hypokalaemia: 2.7 mmol/L (3.2–5.0) and metabolic alkalosis with a partially compensated respiratory acidosis (pH: 7.46, HCO_3^-: 40 mmol/L, PCO_2: 54.6 mmHg). The intact parathyroid hormone (PTH) was low-normal (3.3 pmol/L (1.6–7.5)). Other investigations for a PTH-independent hypercalcaemia are included in Table 1. The serum 25-hydroxyvitamin D level returned high at 212 nmol/L (≥50) in the absence of Vitamin D supplementation. The 1,25-dihydroxyvitamin D was performed on day 10, after treatment of hypercalcaemia (corrected calcium 2.27 mmol/L), and returned slightly above the reference range at 205 pnmol/L (60–200). With her history of prior malignancy (and preceding her history of significant Quick-Eze ingestion), a CT chest/abdomen/pelvis and pelvic and thyroid ultrasounds were performed,

Table 1 Blood results during admission and post-discharge.

Investigation	Day of admission	Other results during admission	Day 5 post-discharge	Reference range
Serum				
Sodium, mmol/L	129		137	135–145
Potassium, mmol/L	2.7		3.7	3.2–5.0
Urea, mmol/L	15.3		7.6	3.5–8.0
Creatinine, μmol/L	171		90	45–90
Estimated GFR, mL/min/1.72 m²	27		59	≥90
Bicarbonate, mmol/L	35		22	22–32
Corrected calcium, mmol/L	4.57		2.26	2.15–2.55
Phosphate, mmol/L	0.59		0.89	0.75–1.50
PTH, pmol/L	3.3			1.6–7.5
25-OH vit D, nmol/L	212			≥50
1,25-OH vit D, pmol/L		205		60–200
ACE, U/L	23			20–70
TSH, mIU/L		1.26		0.4–4.0
Free T4, pmol/L		13.8		9–19.0
ACTH, pmol/L		<1.1		0–12.0
Random cortisol, nmol/L		173*		
Myeloma screen		Negative		
VBG				
pH	7.46			7.30–7.40
pO2, mmHg	25			
pCO2, mmHg	54.6			40.0–50.0
Bicarbonate, mmol/L	40			23–29
Base excess, mmol/L	14			−3.0 to 3.0
Lactate, mmol/L	0.6			≤2

*The random cortisol was collected at 1245 h.
1,25-OH vit D, 1,25-dihydroxyvitamin D; 25-OH vit D, 25-hydroxyvitamin D; ACE, Angiotensin converting enzyme; ACTH, Adrenocorticotropic hormone; GFR, glomerular filtration rate; PTH, Parathyroid hormone; TSH, Thyroid-stimulating hormone.
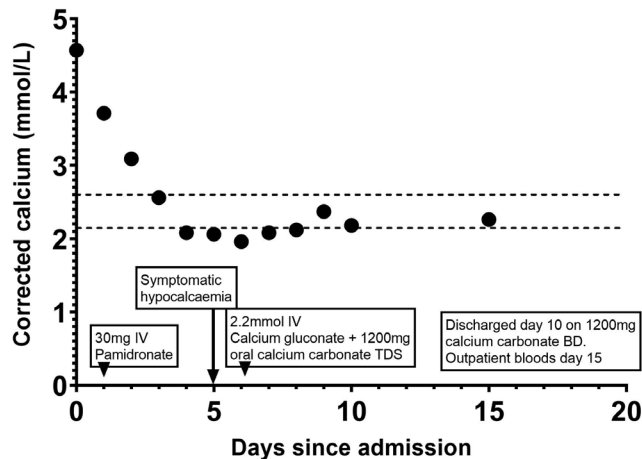
Figure 1

Trend of corrected calcium. The laboratory reference ranges for corrected calcium (2.15–2.55 mol/L) are marked by dashed lines.

which excluded obvious malignancies or granulomatous processes. A baseline corrected calcium 4 years prior was normal at 2.37 mmol/L.

Treatment

The patient was managed initially with 6 L of i.v. crystalloid fluids over the first 48 h, i.v. electrolyte replacement and a single dose of 30 mg i.v. pamidronate (renally adjusted). Serum calcium had normalised by day 3 of admission, and the patient developed symptomatic hypocalcaemia with acral paraesthesia 4 days following the pamidronate dose, reaching a nadir calcium level of 1.96 mmol/L (Fig. 1). PTH at the time of hypocalcaemia was appropriately elevated at 23.6 pmol/L. The hypocalcaemia was managed with 1.2 g PO calcium carbonate TDS and 2.2 mmol i.v. calcium gluconate. She was discharged on day 10 when her corrected calcium had normalised to 2.18 mmol/L, with 1.2 g calcium carbonate twice daily.

Outcome and follow-up

Follow-up biochemistry at day 5 post-discharge showed normalisation of renal function and corrected calcium level at 2.26 mmol/L, and calcium supplementation was ceased shortly after.

Discussion

Hypercalcaemia in MAS is a consequence of calcium input via dietary intake and intestinal absorption exceeding renal excretion (3). Although the amount of calcium required to cause MAS is generally thought to be more than 4 g per day, there have been reports at intakes as low as 1.0–1.5 g per day in pre-existing risk factors including renal impairment, hyperemesis gravidarum and eating disorders (1, 4). A retrospective audit of inpatients with hypercalcaemia without end-stage renal failure demonstrated that MAS was the third leading cause of admission for hypercalcaemia, after hyperparathyroidism and malignancy, at an incidence of 8.8–12% (4, 5) A 1965 study further characterised the syndrome into acute, subacute and chronic forms depending on the duration of ingestion of calcium and alkali (6). This is now thought to represent the same disease spectrum. Compared to the acute form, resolution of hypercalcaemia and renal failure in chronic MAS was slower and there were more features of systemic calcification such as band keratopathy and nephrocalcinosis (6). One case series demonstrated that a high proportion of MAS present with severe hypercalcaemia (corrected serum calcium >3.5 mmol/L) (4), with some cases of hypercalcaemia as high as 5.6 mmol/L (5). Our patient ingested 3.6 g of elemental calcium daily from supplements alone, but no Vitamin D supplementation. MAS typically presents with a PTH-independent hypercalcaemia, renal impairment, metabolic alkalosis and normal or low phosphate levels (7). In response to hypercalcaemia in MAS, calcium-sensing receptors (CaSRs) are activated in the ascending loop of Henle, leading to increased renal calcium excretion and reduced sodium chloride reabsorption (8). This results in volume depletion and a hypochloraemic metabolic alkalosis. Additionally, activated CaSRs in the distal convoluted tubules reduces expression of aquaporin 2 water channels, thereby reducing water reabsorption and promoting a nephrogenic diabetes insipidus (8). Metabolic alkalosis also stimulates the transient receptor potential vanilloid member 5 (TRPV5) which further increases calcium reabsorption (8). Hypercalcaemia has additional deleterious effects in afferent arteriole constriction and reduction of the glomerular filtration rate, intravascular depletion through aforementioned diuresis and reduction in bicarbonate excretion, all of which culminate in renal failure (1, 9).

Pre-existing renal impairment, volume depletion and thiazide diuretics are risk factors for the development of MAS (1). Thiazides reduce calcium excretion by inhibiting the thiazide-sensitive sodium chloride cotransporter and contribute to alkalosis. In the elderly, there is net efflux of calcium from the bone, rendering bone less able to buffer excess calcium. Ageing also leads to impaired ability to excrete excess calcium, possibly due to down-regulation of the CaSRs, further rendering them susceptible to hypercalcaemia (3).

Endocrinology,
Diabetes & Metabolism
CASE REPORTS

M Wang and others

Milk-alkali syndrome

ID: 20-0028; May 2020
DOI: 10.1530/EDM-20-0028

Increased calcium intake usually leads to decreased 25-hydroxylation of vitamin D in the kidneys, resulting in 1,25-dihydroxyvitamin D mediated reduction in intestinal calcium absorption (3). However, if renal excretory capability is overwhelmed, hypercalcaemia would still ensue. In some individuals the failure to fully suppress 1,25-dihydroxyvitamin D levels in the setting of high oral intake may contribute to MAS (3). Our patient exhibited unusually high 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels without oral supplementation. Neither were endogenous causes for excessive production of 1,25-dihydroxyvitamin D such as granulomatous disorders or lymphomas excluded, nor was there a suggestion of a congenital syndrome, such as idiopathic infantile hypercalcaemia. 1,25-dihydroxyvitamin D is generally low in MAS due to suppression of PTH. Nevertheless, the 1,25-dihydroxyvitamin D level was accessed on day 10, when calcium levels had normalised after a period of high PTH in response to hypocalcaemia. PTH mediates upregulation of renal 1α-hydroxylase transcription and may explain the elevated 1,25-dihydroxyvitamin D (10).

Management consists of cessation of calcium supplements and i.v. rehydration, but rebound hypocalcaemia with elevated PTH can occur and is a typical feature of MAS (5). This is distinct from hypercalcaemia of malignancy and hyperparathyroidism, where often there is resistant hypercalcaemia. Bisphosphonates should be avoided in MAS, although, as in our case, the diagnosis is not always clear at the time of presentation.

This case highlights the importance of recognising milk-alkali syndrome as a differential for a PTH-independent hypercalcaemia, especially as it is the third most common cause of admission for hypercalcaemia. The effect of over-the-counter calcium supplementation on the development of hypercalcaemia should not be underestimated. Treatment of MAS with standard calcium-lowering therapy can precipitate hypocalcaemia thereby requiring calcium replacement, as distinct from other aetiologies of hypercalcaemia.

References

1 Medarov BI. Milk-alkali syndrome. *Mayo Clinic Proceedings* 2009 **84** 261–267. (https://doi.org/10.1016/S0025-6196(11)61144-0)

2 Picolos MK, Sims CR, Mastrobattista JM, Carroll MA & Lavis VR. Milk-alkali syndrome in pregnancy. *Obstetrics and Gynecology* 2004 **104** 1201–1204. (https://doi.org/10.1097/01.AOG.0000128109.44291.e2)

3 Felsenfeld AJ & Levine BS. Milk alkali syndrome and the dynamics of calcium homeostasis. *Clinical Journal of the American Society of Nephrology* 2006 **1** 641–654. (https://doi.org/10.2215/CJN.01451005)

4 Picolos MK, Lavis VR & Orlander PR. Milk-alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) inpatients. *Clinical Endocrinology* 2005 **63** 566–576. (https://doi.org/10.1111/j.1365-2265.2005.02383.x)

5 Beall DP & Schofield RH. Milk-alkali syndrome associated with calcium carbonate consumption. Report of 7 patients with parathyroid hormone levels and an estimate of prevalence among patients hospitalized with hypercalcemia. *Medicine* 1995 **74** 89–96. (https://doi.org/10.1097/00005792-199503000-00004)

6 McMillan DE & Freeman RB. The milk alkali syndrome: a study of the acute disorder with comments on the development of the chronic condition. *Medicine* 1965 **44** 485–501. (https://doi.org/10.1097/00005792-196511000-00002)

7 Patel AM, Adeseun GA & Goldfarb S. Calcium-alkali syndrome in the modern era. *Nutrients* 2013 **5** 4880–4893. (https://doi.org/10.3390/nu5124880)

8 Arroyo M, Fenves AZ & Emmett M. The calcium-alkali syndrome. *Proceedings* 2013 **26** 179–181. (https://doi.org/10.1080/08998280.2013.11928954)

9 Timilsina B, Tachamo N, Parajuli PR & Gabriely I. Acute milk-alkali syndrome. *Endocrinology, Diabetes and Metabolism Case Reports* 2018 **2018** 18–75. (https://doi.org/10.1530/EDM-18-0075)

10 Zierold C, Nehring JA & DeLuca HF. Nuclear receptor 4A2 and C/EBPbeta regulate the parathyroid hormone-mediated transcriptional regulation of the 25-hydroxyvitamin D3-1alpha-hydroxylase. *Archives of Biochemistry and Biophysics* 2007 **460** 233–239. (https://doi.org/10.1016/j.abb.2006.11.028)