

Another case of milk-alkali syndrome or a learning opportunity?

Sophie Bondje^{ID}, Camilla Barnes and Felicity Kaplan

Lister Hospital, Stevenage, UK

Correspondence
should be addressed
to S Bondje

Email
sophie.bondje@nhs.scot

Summary

Milk-alkali syndrome (MAS) is a triad of hypercalcaemia, metabolic alkalosis and renal insufficiency. In this study, we present a case of milk-alkali syndrome secondary to concurrent use of over-the-counter (OTC) calcium carbonate-containing antacid tablets (Rennie®) for dyspepsia and calcium carbonate with vitamin D3 (Adcal D3) for osteoporosis. A 72-year-old woman presented with a 2-day history of nausea, vomiting, epigastric pain, constipation, lethargy and mild delirium. Past medical history included osteoporosis treated with daily Adcal D3. Initial blood tests showed elevated serum-adjusted calcium of 3.77 mmol/L (normal range, 2.2–2.6) and creatinine of 292 µmol/L (45–84) from a baseline of 84. This was corrected with i.v. pamidronate and i.v. fluids. She developed asymptomatic hypocalcaemia and rebound hyperparathyroidism. Myeloma screen, vasculitis screen and serum angiotensin-converting enzyme (ACE) were normal, while the CT of the chest, abdomen and pelvis showed renal stones but no malignancy. A bone marrow biopsy showed no evidence of malignancy. Once the delirium resolved, we established that prior to admission, she had been excessively self-medicating with over-the-counter antacids (Rennie®) as required for epigastric pain. The increasing use of calcium preparations for the management of osteoporosis in addition to easily available OTC dyspepsia preparations has made MAS the third most common cause of hypercalcaemia hospitalisations. Educating patients and healthcare professionals on the risks associated with these seemingly safe medications is required. Appropriate warning labels on both calcium preparations used in the management of osteoporosis and OTC calcium-containing preparations would prevent further similar cases and unnecessary morbidity and hospital admission.

Learning points:

What is known?

- An association between high-dose calcium supplementation and hypercalcaemia crisis has been seen in case studies.
- After as little as 1 week of excessive calcium carbonate ingestion, patients can present with symptomatic hypercalcaemia, acute renal failure and metabolic alkalosis (1).
- Women aged 50 and younger need 1 g of calcium per day, while aged 51 and older need 1.2 g (1).
- Although the amount of calcium required for 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 (2).

What this study adds?

- The danger of excessive ingestion of antacid is not adequately highlighted to prescribers and patients.
- Appropriate warning labels on OTC calcium-containing preparations could prevent unnecessary morbidity and hospital admission.



Background

Milk-alkali syndrome (MAS) is a triad of hypercalcaemia, metabolic alkalosis and renal insufficiency. It was originally discovered in the 1930s after treatment of peptic ulcer disease with sodium bicarbonate and milk. In 2006, Beall *et al.* described a 'modern version' showing an association with ingesting vast quantities of calcium carbonate (3). The increasing use of calcium preparations for the management of osteoporosis in addition to easily available OTC dyspepsia preparations has made MAS the third most common cause of hypercalcaemia hospitalisations (4). The other two primary causes are malignancy and primary hyperparathyroidism. Ingestion of large doses of calcium carbonate results in absorption via the passive pathway, an overspill pathway when 1,25 (OH)₂D-dependent calcium transport is at maximum saturation. Around 15% of all calcium absorption is passive, a process likely to have occurred in our patient (2). In this study, we present a case of milk-alkali syndrome secondary to concurrent use of over-the-counter (OTC) calcium-containing antacid tablets (Rennie®) for dyspepsia and calcium carbonate with vitamin D3 (Adcal D3) for osteoporosis.

Case presentation

A 72-year-old woman presented to the hospital with a 2-day history of nausea, vomiting, epigastric pain, constipation, lethargy and delirium. Past medical history included osteoporosis, rheumatoid arthritis, hypothyroidism, chronic obstructive pulmonary disease, chronic kidney disease stage 3 (baseline eGFR, 58 mL/min) and pancreatic insufficiency. Her regular medication was recorded as 1500 mg calcium carbonate with 400 units cholecalciferol (Adcal D3) daily, cholecalciferol (Fultium-D3) 800 units OD, amitriptyline 10 mg OD, pancreatin (Creon) 4000 for three times daily (TDS), levothyroxine 75 µg OD, mirtazapine 15 mg OD and omeprazole 20 mg OD. She subsequently reported using OTC antacid tablets (Rennie®) containing calcium carbonate 680 mg and magnesium carbonate 80 mg per tablet to help alleviate dyspepsia symptoms. The maximum recommended dose is 10 tablets/day, equivalent to calcium carbonate 7.5 g/day equivalent to 3 g of elemental calcium/day. The patient had used these tablets in addition to her regular medications for a few weeks but was unsure of the exact number taken on a daily basis. Examination revealed dehydration and delirium with an abbreviated mental test score of 3/10.

Investigation

The serum-adjusted calcium was elevated at 3.77 mmol/L (normal range, 2.2–2.6), creatinine 292 µmol/L (45–84) from a baseline of 84 and urea 18.4 mmol/L from a baseline of 7 mmol/L. The creatinine rose to 363 µmol/L on day 3 of admission. Vitamin D and phosphate levels were normal at 102.7 nmol/L and 1.51 mmol/L, respectively. The parathyroid hormone (PTH) was initially low at 0.85 pmol/L (1.48–7.63). A venous blood gas showed a metabolic alkalosis (pH: 7.451, pCO₂: 5.72 kPa, HCO₃: 27.8 mmol/L, BE: 3.1 mmol/L and lactate: 1.13 mmol/L).

Treatment

Following treatment with i.v. normal saline (4 L/day for the first 5 days from admission) and 60 mg of i.v. pamidronate, the patient developed transient asymptomatic hypocalcaemia (1.93 mmol/L) with an associated rebound in PTH to 25.02 pmol/L. The adjusted calcium was normalised to 2.25 mmol/L by day 14. Her acute kidney injury resolved over a few days. Myeloma screen, vasculitic screen and serum angiotensin-converting enzyme were normal, while a CT of the chest, abdomen and pelvis showed a non-obstructive 4 mm renal calculus but no malignancy. A bone marrow biopsy showed no evidence of malignancy. Once the patient's delirium resolved, we established that she had been self-medicating with significant quantities of Rennie® tablets for epigastric pain relief in the weeks prior to admission. Her calcium remained normal at 2.34 mmol/L, eGFR at 54 mL/min and PTH at 2.76 pmol/L 2 months post discharge.

Discussion

MAS is now a common cause of hypercalcaemia, along with primary hyperparathyroidism and malignancy. A study of 100 patients admitted to hospital with hypercalcaemia in 1990 showed this syndrome accounted for fewer than 2% of cases. This rose to 12% by 1993. The modern focus on the prevention of osteoporosis and dyspepsia relief has made calcium carbonate preparations readily available as prescriptions and OTC. There is a lack of information available to patients and healthcare professionals warning of the possible consequences of excessive usage, especially for those taking multiple forms of calcium carbonate for different purposes (5).

According to the National Osteoporosis Foundation in 2020, the recommended daily allowance for elemental calcium varies depending on age and gender. Women aged



50 and younger need 1 g and aged 51 and older need 1.2 g of calcium per day (6).

MAS is thought to occur with ingestion of at least 4 g of elemental calcium per day (7). Each Rennie® tablet contains 680 mg of calcium carbonate, and the recommended dose is 1–2 tablets up to three to four times a day. Adcal D3 contains 1.5 g of calcium carbonate, equivalent to 600 mg of elemental calcium per tablet. After as little as 1 week of calcium carbonate treatment, patients can present with symptomatic hypercalcaemia, acute renal failure and metabolic alkalosis (1).

A detailed patient history, including current and previous medications and any OTC preparations, may expedite the diagnosis of MAS, although the differential diagnosis of hypercalcaemia always needs consideration. Compared to other causes of hypercalcaemia, a unique trend is seen with MAS after correction with i.v. saline: hypocalcaemia with a rebound rise in PTH. The measurement of PTH prior to treatment is thus very useful (5).

MAS hypercalcaemia is a consequence of calcium intake via diet or medication, as well as intestinal absorption of calcium exceeding its renal excretion (7). Most calcium absorption is dependent on 1,25(OH)₂D-dependent calcium transport. The passive pathway becomes the major conduit for calcium absorption when excessive calcium is consumed (2).

There are currently limited data on vitamin D and pre-existing renal impairment in MAS. Under normal circumstances, high renal calcium excretion is closely aligned to increased intestinal calcium absorption with suppression of 1,25(OH)₂D levels. In our case, the large quantities of continuously ingested calcium have blocked renal excretory capacity and resulted in predicted hypercalcaemia due to failure to properly suppress 1,25(OH)₂D levels (8).

Management of MAS is conservative, including the discontinuation of calcium preparations and i.v. saline administration. Our patient was given pamidronate inappropriately before the cause for hypercalcaemia was identified. Educating patients and healthcare professionals about the risks associated with these seemingly safe medications is required. Appropriate warning labels on OTC calcium-containing preparations would help prevent further cases of this nature (5).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article.

Author contribution statement

S Bondje and C Barnes wrote the manuscript and were involved in the diagnosis and management of the case. F Kaplan was involved in the diagnosis and management of the case and reviewed the manuscript.

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