

Lessons of the month: Over-the-counter antacids causing hypercalcaemia: The emergence of calcium-alkali syndrome

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ABSTRACT

We present the case of a woman who was found to have severe hypercalcaemia, staghorn calculus formation and renal impairment from the long-standing ingestion of calcium carbonate antacids from a supermarket outlet. The dosage was reported to be approximately 1,800 mg of elemental calcium each day which would constitute only a marginal increase on the recommended intake for daily elemental calcium. Furthermore, she was concomitantly taking a prescribed anti-hypertensive medication that may have exacerbated the hypercalcaemia and subsequent renal calcification. While calcium-alkali syndrome is well documented, it can be overlooked by clinicians as the predominant cause of hypercalcaemia, especially if a thorough drug history is not actively sought. This is particularly important as calcium carbonate products are increasingly being purchased as over-the-counter remedies for dyspepsia management as well as osteoporosis prevention. Explicit product labelling regarding limiting duration usage, potential drug interactions and risk of calcification is therefore recommended.

KEYWORDS: Hypercalcaemia, antacids, alkalosis, calcium-alkali syndrome, calculus

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Introduction

Incidental hypercalcaemia is a common clinical finding and the differentials, although wide, are usually due to either primary hyperparathyroidism or hypercalcaemia of malignancy. Over the last 2 decades, hypercalcaemia from the ingestion of prescribed and over-the-counter calcium-alkali medications has become increasingly prevalent.

Milk-alkali syndrome and its contemporary counterpart

Milk-alkali syndrome is a distinctive disease process caused by the ingestion of large amounts of calcium and absorbable

alkali resulting in hypercalcaemia.¹ If left unchecked, metastatic calcification, alkalosis and irreversible renal failure can ensue.¹ First described in the 1920s, it was principally caused by the administration of milk and bicarbonate for the treatment of peptic ulcers under what was popularised as the Sippy regimen.²

With the introduction of agents that reduce acid secretion, chiefly histamine-2-blockers and proton pump inhibitors, the incidence of milk-alkali syndrome steadily declined.³ In recent years, however, increasing use of calcium carbonate, mostly for osteoporosis prevention, has led to a resurgence of this condition.³ Indeed, the term calcium-alkali syndrome better reflects this evolving phenomenon.

The pathogenesis of calcium-alkali syndrome is complex. Although increased calcium intake is a prerequisite for this clinical manifestation, the critical abnormality relates to the kidneys' reduced ability to excrete calcium.⁴ The latter being caused by renal vasoconstriction (a direct effect of hypercalcaemia) as well as increased tubular reabsorption of calcium from an alkalotic environment. Increased bicarbonate absorption from the tubules perpetuates the alkalosis resulting in stone formation and renal impairment if left unchecked.⁴ Commonly used medication such as thiazide diuretics, renin-angiotensin inhibitors and non-steroidal anti-inflammatory drugs can also influence calcium retention and predispose some people to calcium-alkali syndrome.⁵

Between 1,000–1,200 mg of daily elemental calcium in combination with 800–1000 IU of vitamin D is required to maintain adequate bone health in the majority of adults. Cases of calcium-alkali syndrome have been reported from the ingestion of less than 2 g of elemental calcium each day; a dose not much higher than current recommended intake guidance.⁵

We present the case of a woman found to have severe hypercalcaemia from the chronic ingestion of over-the-counter antacid medication that was reported to be just 1,800 mg of elemental calcium each day.

Case presentation

A 47-year-old woman underwent routine blood tests to investigate the cause of a newly diagnosed large staghorn calculus (Fig 1). As part of her workup, she was noted to have a significantly elevated corrected calcium of 3.50 mmol/L (normal range 2.20–2.60). This had been normal when last checked 2 years earlier. Apart from her renal stone, she denied any symptoms attributable to hypercalcaemia such as generalised aches, fatigue, abdominal pain, constipation or osmotic symptoms.

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Fig 1. Axial section computed tomography demonstrating opacification of right pelvicalyceal system.

Past medical history included a diagnosis of progressive cerebellar syndrome, hypertension, mechanical lower-back pain and gastro-oesophageal reflux disease. Regular prescribed medication included losartan, simvastatin, paracetamol and a buprenorphine analgesic patch.

In light of the severe hypercalcaemia, she was urgently assessed by the medical team and a detailed laboratory work-up was undertaken that included a normal full blood count, total protein, phosphate, alkaline phosphatase, inflammatory markers and myeloma screen. She was noted to be vitamin D insufficient. Renal function revealed an eGFR of 45 mL/min/1.73 m² (previously normal when checked 1 year earlier). Venous blood gas confirmed an elevated ionised calcium of 1.63 mmol/L (normal range 1.150–1.330) and a borderline normal pH of 7.43 (normal range 7.35–7.45). Her parathyroid hormone level was also noted to be appropriately suppressed at 1.5 pmol/L (normal range 1.6–6.9).

On further enquiry the patient admitted to ingesting up to nine tablets of calcium carbonate (4,500 mg in total) every day for 2 years. This approximated to 1,800 mg of elemental calcium. She had bought this medication from a supermarket for the treatment of her longstanding dyspepsia and had never sought advice from her doctor.

The patient was asked to cease her calcium carbonate and commenced on lansoprazole for her reflux symptoms. She was also asked to increase her fluid intake to 3 litres per day and reviewed the following day to recheck her calcium level. This had dropped to 3.25 mmol/L. Over the subsequent days, her calcium continued to fall and, when checked one month later, had completely normalised with a corresponding normalisation of parathyroid hormone level.

She was reviewed by the urology team for the definitive management of her renal stone and subsequently underwent a percutaneous nephrolithotomy. This was complicated by the development of a postoperative haematoma.

Pathological analysis of the calculus revealed it to be predominantly calcium phosphate in composition.

Discussion

Chronic high-dose calcium carbonate ingestion resulted in hypercalcaemia, renal dysfunction and nephrolithiasis in our patient. The crystallisation of a large calcium phosphate stone was presumably secondary to an abnormally elevated urine pH.⁶ While the ingestion of a marginally raised dosage of calcium carbonate antacid therapy over a long duration was critical in the pathogenesis of hypercalcaemia and stone formation, the patient may have been particularly susceptible since she was concomitantly taking an angiotensin receptor antagonist (losartan) for hypertension. Such drugs are known to reduce glomerular filtration rate and may have further exacerbated the ability of the kidneys to excrete calcium.

Calcium-alkali syndrome may be easily overlooked by physicians, despite it being recognised as the third commonest cause of hypercalcaemia; after primary hyperparathyroidism and malignancy. It is therefore imperative to take a detailed drug history which should include a record of over-the-counter medications. Although the patient in this case did not exceed the specified dosage for the treatment of her dyspepsia, the adverse effects were brought about by chronic consumption of calcium carbonate at a modestly higher dose than the usual recommended dietary allowance.

Over-the-counter calcium carbonate antacids must contain explicit instructions for consumers to use for short durations only. Furthermore, specific product labelling is recommended in order to highlight the potential interaction with anti-hypertensives such as thiazide diuretics or inhibitors of the renin-angiotensin system (RAS). This is particularly important since many antacid products can be directly bought from supermarket shelves with little in the way of restriction or safeguard. ■

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