

# Antacid-induced acute hypercalcemia: An increasingly common and potentially dangerous occurrence

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## Abstract

Hypercalcemia is frequently encountered in both hospital wards and the primary care setting; 90% of cases can be attributed to primary hyperparathyroidism and malignancy. However, a minority are caused by medications, of which calcium supplements have been an increasingly common etiology. We are presenting a case of hypercalcemia resulted after acute oral intake of a moderate amount of antacids (calcium tablets) and normalized after supplement withdrawal.

## Keywords

Hypercalcemia, calcium supplements, calcium-alkali syndrome

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## Introduction

The milk–alkali regimen was described in the 1920s by Sippy as a treatment for peptic ulcer disease (PUD).<sup>1</sup> It consisted of milk and cream combined with alkali (magnesium oxide, sodium bicarbonate, and bismuth subcarbonate).<sup>1</sup> While milk–alkali was widely embraced as the preferred treatment for PUD, it was eventually linked to side effects such as headache, irritability, lightheadedness, and, at times, nausea and vomiting.<sup>1</sup> In 1949, when the milk–alkali regimen was retrospectively investigated, Burnett et al.<sup>2</sup> noted that all patients developed hypercalcemia, azotemia and renal impairment, and some albuminuria, gastrointestinal symptoms, pruritus, or arthritic complaints. Nowadays, increasing numbers of patients are using calcium carbonate not only as an antacid but also as calcium supplementation, especially when postmenopausal, on corticosteroid therapy or in renal failure.<sup>1</sup> Calcium carbonate, which is alkaline, is a major source of calcium and alkali.<sup>1</sup> This has led to the reemergence of the so-called “milk-alkali syndrome” aka “calcium-alkali syndrome,” characterized by hypercalcemia, metabolic alkalosis, and renal failure.<sup>3</sup> The case report will underscore the importance of obtaining a thorough medication history, including over-the-counter supplements. This can help potentially identify causative factors for hypercalcemia and eliminate/reduce them, thereby minimizing the potential complications of hypercalcemia, and obviate the need for time-consuming and expensive investigations.

## Case presentation

A 61-year-old male with a past medical history of type 2 diabetes mellitus (T2DM), hypertension, and hyperlipidemia presented to the office for a regular follow-up. Vital signs were as follows: blood pressure 124/72 mmHg, heart rate 78 bp, respiratory rate 12 bpm, and temperature 98.3 F. The patient was asymptomatic. Family history included T2DM in both parents and cardiovascular disease in his mother, but no history of congenital diseases or malignancies. He denied smoking, alcohol abuse, or illicit drug intake. Home medications consisted of amlodipine, valsartan, atorvastatin, pioglitazone, metformin, insulin detemir, liraglutide, and dapagliflozin. Patient took no calcium, vitamin D supplementation, and no proton pump inhibitors (PPIs) or histamine H<sub>2</sub>-receptor antagonists. No known allergies to medications were reported. Patient stated he had been properly hydrating himself. He denied palpitations, fatigue, abdominal pain, polyuria, impaired concentration, constipation, dysuria, flank

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pain or a history of nephrolithiasis, weight loss, night sweats, dyspnea, cough, and rash. He also denied smoking, drinking alcohol, or using recreational drugs. Physical examination was unremarkable, and vital signs were within normal levels. There was no evidence of dehydration. Patient underwent laboratory testing the day prior to being seen. Results were significant for calcium 11.1 mg/dL, albumin 4.7 g/dL, blood urea nitrogen (BUN) 21 mg/dL, creatinine 0.91 mg/dL, chloride 101 mmol/L, and fasting glucose 139 mg/dL. Careful history revealed that, the evening prior the blood draw, the patient experienced an unusual episode of sudden-onset epigastric burning and took six chewable tablets of Tums 200 mg calcium (500 mg). Patient denied taking Tums on a regular basis and had not had any in weeks. Patient was asked to refrain from ingesting Tums or any other over-the-counter antacid medication and increase oral hydration. Given the mild elevation in calcium and the lack of palpitations or tachycardia, an electrocardiography was not ordered. Five days later, he went for repeat blood work. By this time, calcium normalized to 9.3 mg/dL, thus ruling out hyperparathyroidism. Ionized calcium and parathyroid hormone intact were 4.8 mg/dL and 54 pg/mL, respectively. Urine protein electrophoresis and serum protein electrophoresis did not detect any monoclonal proteins. Of note, patient never had an event of hypercalcemia, either before or after this episode.

## Discussion

While 90% of cases of hypercalcemia can be attributed to primary hyperparathyroidism and malignancy,<sup>4</sup> calcium supplements have been an increasingly common etiology.<sup>5</sup> Dyspepsia and gastroesophageal reflux disease (GERD) are estimated to be encountered in approximately 21% and 13% of the world population, respectively.<sup>6,7</sup> Given the overall trend of stepping away from excessive usage of PPIs secondary to adverse side effects such as acute interstitial nephritis, fractures, and *Clostridium difficile*-associated diarrhea, increasing numbers of patients are resorting to using calcium carbonate both as an antacid and as a calcium supplement to help treat or prevent osteoporosis.<sup>3,8</sup> While over-the-counter medications are believed to be safe and hypercalcemia only usually occurs after ingestion of more than 4 g of calcium per day,<sup>9</sup> previous studies have argued that some patients might be more prone to this occurrence, even when ingesting dosages below the daily limit recommended by the manufacturer.<sup>10</sup>

Hypercalcemia has been proven to decrease glomerular filtration and increase sodium excretion in the urine, thus leading to decreased intravascular volume and alkalosis.<sup>9</sup> The milk-alkali syndrome, consisting of hypercalcemia, metabolic alkalosis, and renal impairment, has now become the third most common cause of in-hospital hypercalcemia, after primary hyperparathyroidism and malignant neoplasms, and it is estimated to be encountered in 9% to 12% of hypercalcemic patients.<sup>1</sup> Among patients with severely

elevated calcium (>14 mg/dL), milk-alkali syndrome is in fact more frequently responsible than malignancies and can lead to long-lasting renal impairment.<sup>1</sup> Symptoms of milk-alkali syndrome can develop anywhere from as little as several days to months after initiation of therapy.<sup>1</sup>

Antacid-induced hypercalcemia should be a differential diagnosis when a patient presents with elevated calcium levels. A careful medication history, including over-the-counter supplements, should be taken. As seen hereby, using over-the-counter antacid therapy does not guarantee absolute safety profile as even acute ingestion of moderate doses can potentially bring about sudden spikes in calcium level.<sup>9</sup> Timely medication withdrawal and increased hydration can minimize progression to calcium-alkali syndrome and decrease the need for the more expensive investigations required in the workup of malignancy and hyperparathyroidism.<sup>4</sup>

## Conclusion

Clinicians must keep a high index of suspicion in any patient who presents with asymptomatic hypercalcemia and perform thorough reconciliation of all medications, including those available over-the-counter. Although antacids are considered safe, hypercalcemia can occur. Physicians should educate patients on the risks associated with antacid ingestion.

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## Informed consent

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