CASE REPORT

Hypercalcaemia and acute kidney injury following administration of vitamin D in granulomatous disease

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SUMMARY

Vitamin D deficiency is common. It causes osteomalacia, may contribute to osteoporosis and is an independent risk factor for cancer, diabetes, multiple sclerosis, cardiovascular disease and all-cause mortality. We describe patients with a history of sarcoidosis who developed acute kidney injury due to hypercalcaemia following treatment with colecalciferol.

BACKGROUND

There is no doubt that the interest in vitamin D has escalated over the past few years.¹ On the background of numerous studies,^{2–7} many physicians believe it to be a new miracle cure. Prescribing vitamin D replacement has found its place in modern medicine. There is little written about the potential of something so cheap and seemingly innocuous to cause harm.

Vitamin D deficiency is prevalent in the Asian population in northern latitudes. There is also increased prevalence of granulomatous disease within this group. This case shows that vitamin D replacement can be potentially hazardous and should be undertaken with care.

CASE PRESENTATION

A 38-year-old Pakistani man reported with weight loss and abdominal pain in October 2000. Investigations included serum creatinine 210 $\mu\text{mol/L}$, calcium 2.42 mmol/L and ACE 339 IU/L. Chest X-ray and ultrasound scan of the kidneys were normal. Oesophagogastrosocopy showed mild gastritis. Gastric mucosal biopsy revealed non-caseating granulomas. Renal biopsy showed granulomatous interstitial nephritis. He was treated with antituberculous therapy and prednisolone. Subsequently, culture of three early morning urines did not grow acid-fast bacilli. His abdominal symptoms settled, serum creatinine decreased to approximately 140 $\mu\text{mol/L}$ and serum calcium remained normal for 9 years. Serum ACE remained moderately elevated between 87 and 158 IU/L despite prednisolone and azathioprine. In August 2011, he had a cholecystectomy when serum creatinine was 156 $\mu\text{mol/L}$ and calcium 2.25 mmol/L . In January 2012, he felt non-specifically unwell. Serum creatinine was 282 $\mu\text{mol/L}$, calcium 2.39 mmol/L and 25-hydroxyvitamin D 3.7 ng/mL . He was prescribed 60 000 IU of oral colecalciferol for 3 days. Three weeks later, he reported with leg cramps, nausea, vomiting and constipation. Serum calcium was 3.77 mmol/L , creatinine 505 $\mu\text{mol/L}$, parathyroid hormone (PTH) <0.3 pmol/L and ACE 232 IU/L. Serum immunoglobulins, tumour markers,

urine culture, chest X-ray, renal ultrasound scan and skeletal survey were normal. CT of the thorax revealed a mild fibrotic process but there was no lymphadenopathy. He was treated with intravenous normal saline, pamidronate and prednisolone. His serum creatinine decreased to 220 $\mu\text{mol/L}$.

We have been referred two other patients with acute kidney injury associated with hypercalcaemia recently. Both were of south Asian origin, had known sarcoidosis with a raised serum ACE and had been prescribed similar large doses of colecalciferol for vitamin D deficiency.

DISCUSSION

25-Hydroxyvitamin D assays are now widely available, and many guidelines recommend treating vitamin D deficiency with larger doses of colecalciferol than in the past.⁸ These patients developed hypercalcaemia and acute kidney injury following the prescription of recommended doses of colecalciferol. They had all been diagnosed with sarcoidosis several years earlier, but the significance of this was not appreciated. The link between sarcoidosis, vitamin D and hypercalcaemia was first recognised in 1939, when administration of one pint of cod liver oil per month to patients with known sarcoid caused hypercalcaemia.⁹ A similar link has been described in active tuberculosis¹⁰ and Hodgkin's disease.¹¹

Until recently, iatrogenic hypercalcaemia had been unusual because high dose vitamin D supplements were seldom prescribed. This has changed with increased availability of 25-hydroxyvitamin D assays, belief in pleiotropic advantages of vitamin D replacement and guidelines which recommend large doses of colecalciferol.

Normally vitamin D₂/D₃ produced by the skin or absorbed from food is converted by the liver to 25-hydroxyvitamin D and then by 1- α hydroxylase in the kidney to 1,25-dihydroxyvitamin D. Enzyme activity is tightly regulated by PTH and serum phosphate. It is also indirectly regulated by serum calcium.¹² Large doses of colecalciferol, which is the non-hydroxylated form of vitamin D, do not therefore cause hypercalcaemia in most people. In contrast, the macrophages within sarcoid granulomas synthesise 1,25-dihydroxyvitamin D constitutively without external regulation. In one study, 58 of 59 patients with sarcoidosis had deficient or insufficient 25-hydroxyvitamin D concentrations, although 71% of these patients had normal concentrations of 1,25-dihydroxyvitamin D.¹³

Glucocorticoids inhibit the 1- α hydroxylase activity of macrophages and are the principal

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treatment of hypercalcaemia in sarcoidosis. Thus the administration of corticosteroids protects against the development of hypercalcaemia when colecalciferol is administered. One of our patients did not become hypercalcaemic when given colecalciferol while she was taking prednisolone, but developed severe hypercalcaemia a year later when given colecalciferol after the dose of prednisolone had been reduced to 5 mg/day.

Sarcoidosis is more prevalent in the Asian and Black community. This population subgroup is more likely to be suspected of vitamin D deficiency than Caucasians. They are also more likely to be prescribed supplements.

The diagnosis of sarcoidosis in these three patients had been made many years earlier and was easily overlooked without awareness of the risk. A careful clinical history may have avoided their subsequent renal complications. History alone would not identify patients with undiagnosed granulomatous disease, however. Measurement of serum ACE in high-risk populations could prove a screening test. Alternatively, a normal 1,25-dihydroxyvitamin D concentration despite low 25-hydroxyvitamin D might suggest the diagnosis. However, additional tests have cost implications.

Granulomatous disease must be excluded before treating low 25-hydroxyvitamin D concentrations. Future guidelines for treatment of vitamin D deficiency should include a caution to

exclude sarcoidosis and related granulomatous disease before starting treatment with a recommendation to monitor serum calcium after the administration of colecalciferol.

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Patient consent Obtained.

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Learning points

- Extreme caution should be employed when prescribing vitamin D in patients with known granulomatous disease.
- Exclude granulomatous disease prior to starting vitamin D replacement.
- Measuring serum ACE may prove a valid screening tool for patients thought to have a high risk of granulomatous disease.

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