Risks of the 'Sunshine pill' – a case of hypervitaminosis D

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ABSTRACT

Vitamin D is a fat-soluble vitamin essential for calcium homeostasis and bone health. Vitamin D toxicity or hypervitaminosis D is extremely rare. We describe the case of a 73-year-old man who presented with life-threatening hypervitaminosis D and hypercalcaemia resulting from self-medicated doses of vitamin D supplements. This case, alongside other global case reports, highlights the potential dangers of unlicensed vitamin D replacement. We discuss the evidence for vitamin D replacement and remind readers of the current guidance on daily intake and supplementation.

KEYWORDS: Hypervitaminosis D, vitamin D toxicity, vitamin D supplementation, calcium homeostasis, hypercalcaemia

Case presentation

A 73-year-old man presented with a 4-week history of diarrhoea and 2-week history of confusion. He was a retired nuclear scientist who was previously fully independent with no history of cognitive impairment. There was no history of smoking, alcohol or substance abuse.

His wife reported cognitive disturbances including being unable to use a cassette player or turn on his electric razor and he had started urinating in the sink. He was visited by his GP who found him confused, drowsy and dehydrated. Observations were unremarkable but a rectal examination showed hard stool in the rectum. Presuming a urinary tract infection, laxatives and trimethoprim were prescribed and he was transferred to hospital for further investigations.

On admission there were no infective signs or symptoms. His cardiovascular, respiratory and abdominal examinations were unremarkable. He was extremely delirious requiring sedation and occasional reasonable physical restraint. He scored 3/10 on the Abbreviated Mental Test Score (AMTS) but had no other neurological signs. His electrocardiogram (ECG), chest X-ray (CXR) and computed tomography (CT) brain were all normal. Admission blood test results are shown in Table 1.

Diagnosis

Investigations for his hypercalcaemia revealed low parathyroid hormone 0.6 pmol/L and a toxic 25-hydroxyvitamin D (25[OH]D) concentration 881 nmol/L (normal range 25–100 nmol/L), suggesting a diagnosis of hypervitaminosis D. Other causes of hypercalcaemia such as malignancy, thyroid disease and sarcoidosis were excluded. On further questioning his daughter reported he had been taking 60,000 IU vitamin D capsules per day for the last 2 years having read a book advocating its health benefits.

Table 1. Patient's blood test results on admission

Parameter	Results	Units	Normal values
Haemoglobin	123	g/L	130–180
WBC count	4.4	10^9/L	4–11
Platelet count	168	10^9/L	150–500
RBC count	4.15	10^{12}/L	4.5–6.5
Haematocrit	0.375	L/L	0.38–0.54
MCV	90.2	Fl	76–103
Neutrophils	3.43	10^9/L	1.5–8
Sodium	141	mmol/L	133–146
Potassium	4.2	mmol/L	3.5–5.3
Urea	9	mmol/L	2.5–7.8
Creatinine	202	umol/L	59–104
eGFR	25	mL/min/1.73m^2	60–99
Bilirubin	5	umol/L	0–21
ALT	12	U/L	0–60
ALP	78	U/L	46–116
Albumin	35	g/L	34–50
CRP	<2	mg/dL	<3
Procalcitonin	0.12	ng/mL	<0.25
Calcium	3.06	mmol/L	2.15–2.6
Corrected calcium	3.15	mmol/L	2.2–2.62
Phosphate	1.04	mmol/L	0.8–1.5
Magnesium	0.94	mmol/L	0.7–1
TSH	1.76	mu/L	0.55–4.78
B12	560	ng/L	211–911
Folate	14.76	ug/L	3.38–23.9
Ferritin	18	ug/L	22–322

ALP = alkaline phosphatase; ALT = alanine aminotransferase; CRP = C-reactive protein; MCV = mean corpuscular volume; RBC = red blood cell count; TSH = thyroid stimulating hormone; WBC = white blood cell count

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Initial management

According to **www.toxbase.org** guidelines, he was treated with intravenous fluids followed by a single dose of 60 mg pamidronate. Steroids were considered but not used in this case following discussion with endocrinology department colleagues.

Case progression and outcome

After 1 week of supportive treatment the patient showed signs of improvement with calcium concentrations and renal function now normal. His repeat AMTS was 6/10 as cognitively he started to recover. Two weeks after admission he was back to baseline and discharged home. Weekly blood tests were arranged over the next month to ensure no rebound hypercalcaemia and all vitamin D supplements were discontinued.

Discussion

Vitamin D is a fat-soluble vitamin essential for calcium homeostasis and bone health. Vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol) can be obtained naturally from dietary sources (eg wild mushrooms and oily fish). Vitamin D_3 is also formed by UV-B mediated conversion of 7-Dehydrocholesterol in the skin.[1] Due to a wide therapeutic index hypervitaminosis D is extremely rare; however, there are a small number of global case studies showing it can occur at excessively high doses of supplementation.[2–5] The reported non-musculoskeletal health benefits of vitamin D supplementation,[6,7] including links to sepsis severity,[8] acute respiratory distress syndrome (ARDS)[9] and respiratory tract infections (RTIs)[10] have seen its use increase significantly. There are also widespread claims in non-medical publications and the media that vitamin D supplementation is a 'miracle cure'.[11]

The right amount of vitamin D

The Scientific Advisory Committee on Nutrition (SACN) and the National Institute for Health and Care Excellence (NICE) state that a 25(OH)D concentration below 30 nmol/L qualifies as vitamin D deficient and there are clear links with poor musculoskeletal health.[12,13] Apart from the possible prevention of RTIs,[10] robust evidence linking vitamin D deficiency to non-musculoskeletal diseases such as cancer, cardiovascular disease and obesity is still lacking.[6,7] Autier *et al* suggest that low 25(OH)D concentrations may simply be a marker of ill health rather than primarily causing disease.[14]

Conversely, vitamin D toxicity with hypercalcaemia can cause bone demineralisation and both renal and cardiovascular toxicity.[12] The third National Health and Nutrition Examination Survey (NHANES III) also suggested that vitamin D concentrations higher than 75 nmol/L could be associated with adverse effects, including increased mortality and incidence of cardiovascular disease.[15]

Based on the robust evidence for musculoskeletal outcomes alone, SACN and NICE currently recommend a vitamin D reference nutrient intake (RNI) of 400 IU daily alongside sensible sun exposure for all healthy adults in the UK to prevent vitamin D deficiency. Although there is currently no evidence for an optimal vitamin D status, NICE states that serum 25(OH)D concentrations >50 nmol/L are 'adequate'. For vitamin D deficient adults the maximum dose for supplementation recommended by SACN should not exceed 4,000 IU/day. There are fixed loading regimes recommended by NICE, for example 50,000 IU once a week for 6 weeks (300,000 IU in total), and although these are not expected to cause adverse effects, may cause hypercalcaemia in some individuals.[12,13] 50,000 IU vitamin D capsules are easily purchased on the internet and one has to question whether such high doses should be available to the public without prescription.

Pharmacokinetics and clinical course of hypervitaminosis D

To appreciate the clinical course of hypervitaminosis D, it is important to understand the pharmacokinetics. The lipophilic nature of vitamin D explains its adipose tissue distribution. It has a slow turnover in the body with a half-life of approximately 2 months. Its main transport metabolite, 25(OH)D, has a half-life of 15 days while the more active metabolite, Calcitriol or $1,25(OH)_2D$, has a half-life of 15 hours.[16–18] Therefore, depending on the level of toxicity, it can be expected that patients with hypervitaminosis D may exhibit symptoms for several weeks before showing signs of improvement.

Hypervitaminosis D treatment

The majority of symptoms are due to hypercalcaemia; therefore, the mainstay of successful treatment in case reports has included initial rehydration with intravenous fluids followed by bisphosphonate therapy. Some cases were managed using diuretics, calcitonin or glucocorticoids as second line treatment.[2,3,19] We consulted Toxbase and local endocrinology expertise to guide treatment. Due to the risk of rebound hypercalcaemia and arrhythmias, we monitored biochemical parameters and ECGs regularly. Given the fact that hypervitaminosis D is so rare it is important to also consider and exclude other causes of hypercalcaemia during treatment.

Key learning points

- Hypervitaminosis D is a rare condition and can be life-threatening
- Given the increasing self-supplementation and medical prescriptions of vitamin D, consider hypervitaminosis D as a differential diagnosis in patients presenting with hypercalcaemia
- Refer to the SACN and NICE guidelines for vitamin D intake and supplementation in adults to prevent and treat vitamin D deficiency
- Important for clinicians to understand the pharmacokinetics of vitamin D to help predict the clinical course of patients with hypervitaminosis D
- The mainstay of hypervitaminosis D treatment involves the correction of hypercalcaemia with rehydration and bisphosphonate therapy. ■

Consent

Written informed consent was obtained from the patient's next of kin for the publication of this case report.

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