INTERNAL MEDICINE JOURNAL

Brief Communications

Prolonged vitamin D intoxication: presentation, pathogenesis and progress

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Key words
vitamin D intoxication, hypercalcaemia, acute renal injury.

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Received 26 February 2013; accepted 22 May 2013.

doi:10.1111/imj.12269

Abstract

Vitamin D toxicity from unactivated vitamin D (calciferol) therapy is currently a rare cause of hypercalcaemia. However, the frequency of this event may increase as high-dose unactivated vitamin D preparations become available. Prolonged vitamin D toxicity can cause reversible hypercalcaemia and partially reversible renal impairment. Parathyroid hormone may not be suppressed with unactivated vitamin D toxicity, especially if renal disease coexists.

Hypervitaminosis D has been a rare cause of hypercalcaemia and renal impairment. However, this is likely to become more prevalent as high doses of vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) become available, either prescribed or over the counter. We report a case of hypervitaminosis D with severe acute renal injury due to a prolonged intake of toxic doses of unactivated vitamin D3 therapy, where 600 000 IU was consumed daily for more than 3 years. We describe the biochemical recovery over 5 months of follow up.

A 67-year-old woman presented to an after-hours medical service with a 2-week history of nausea, vomiting and abdominal discomfort. Examination revealed that she was dehydrated and had a body mass index of 16 kg/m^2 (weight 43 kg). The patient was referred to a tertiary hospital renal clinic where review confirmed severe renal impairment with a serum creatinine of 330 µmol/L (reference interval (RI) 50–90 umol/L), equating to an estimated glomerular filtration rate of 13 mL/min/1.73 m^2. This was attributed to hypercalcaemia as the corrected total serum calcium was 3.27 mmol/L (RI 2.25–2.55 mmol/L). Serum intact parathyroid hormone (PTH) was 2.2 pmol/L (RI 1–5.3 pmol/L) and 25 hydroxy vitamin D (25OHD) was 912 nmol/L, measured initially by the polyclonal Roche competitive immunoassay and confirmed with liquid chromatography tandem mass spectrometry, which quantified 25OHD$_3$ as 800 nmol/L (RI 50–150 nmol/L). The patient confirmed vitamin supplementation with 15 mg of cholecalciferol (600 000 IU) daily for just over 3 years. A compounding chemist specially formulated the prescribed multivitamin supplements; however, the cholecalciferol dose was an unintentional transcription error, with 7.5 mg of cholecalciferol (300 000 IU) being prescribed per compounded tablet instead of 7.5 µg (300 IU) of cholecalciferol. Four days after presentation, 25OHD was 770 nmol/L measured by the polyclonal Roche immunoassay. The patient declined specific therapy for hypercalcaemia, but agreed to cease the multivitamin preparation.

The patient's renal function had been unremarkable 3 years previously, and hypercalcaemia induced by vitamin D toxicity was the only cause identified by a consultant nephrologist. There was no clinical evidence of sarcoidosis, mycobacterium infection or other condition associated with dysregulated vitamin D metabolism, which may have predisposed to vitamin D toxicity and hypercalcaemia. Table 1 demonstrates the chronology of serum chemistry results.

Funding: None.
Conflict of interest: None.

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Table 1 Serum chemistry

	Initial	1 month	2 months	4 months	5 months
Creatinine μmol/L (RI 50–90 μmol/L)	330	288	184	155	124
eGFR (mL/min/1.73 m^2)	13	15	25	31	40
Corrected calcium mmol/L (RI 2.25–2.55)	3.27	2.95	2.59	2.57	2.40
25 hydroxy vitamin D nmol/L (RI 50–150)	912	770	597	430	250

eGFR, estimated glomerular filtration rate.

Our case demonstrates the biochemical effects of prolonged exposure to an overdose of unactivated vitamin D therapy, as opposed to brief toxic vitamin D ingestion. The improvement in renal function in our patient (Table 1), while not complete, was encouraging, as the course of severe acute kidney injury from prolonged hypervitaminosis D has not been clearly established. The renal impairment was relatively mild in the cases described by Araki *et al*. where the time course for improvement listed in case two was 4 weeks.[1] The time course and magnitude of improvement in serum creatinine was not specified in the cases of hypervitaminosis D-induced hypercalcaemia described by Lowe *et al*.[2]

Serum PTH was not suppressed in our case, nor was PTH suppressed in two of the nine cases described by Lowe *et al*.[2] Unsuppressed PTH may be due to the coexistence of renal failure and/or hyperphosphataemia, although it is possible that a degree of parathyroid autonomy may also exist. The two cases with non-suppressed PTH described by Lowe *et al*. had the highest serum creatinine; 283 μmol/L and 460 μmol/L respectively. In the cases with suppressed PTH described by Lowe *et al*., the highest serum creatinine was 159 μmol/L.[2] The PTH response to hypercalcaemia may be affected by severe renal impairment induced by hypervitaminosis D.

Hypercalcaemia induced by vitamin D toxicity is responsible for the complications of vitamin D intoxication. Hypercalcaemia is usually not observed with serum 25OHD below 220 nmol/L.[3] Generally, 25OHD concentrations above 600 nmol/L are required to induce hypercalcaemia.[4] There are limited published data on the lowest toxic dose of vitamin D, although Hathcock suggested that an oral daily dose of 10 000 IU of cholecalciferol was unlikely to cause any adverse effects in the healthy population.[4] However, subpopulations could be sensitive to excessive calciferol therapy, as confirmed recently by Schlingmann *et al*. who identified mutations in the 24 hydroxylase gene (CYP24A1), which explained several cases of severe neonatal hypercalcemia and prolonged hypercalcaemia following high-dose bolus unactivated vitamin D therapy.[5] A subsequent study by Dauber *et al*. demonstrated that mutations in CYP24A1 were causal in some but not all cases of neonatal hypercalcaemia.[6] However, all of the described cases with CYP24A1 mutations had suppressed PTH, in contrast to our case.

The aetiology of hypercalcaemia in hypervitaminosis D requires an understanding of vitamin D metabolism and may be dependent on body weight and more specifically, non-lean body mass. Vitamin D is lipophilic and distributed predominantly in adipose tissue with an elimination half-life of approximately 2 months.[7] Vitamin D is hydroxylated in the mitochondria to 25OHD, which is the major circulating vitamin D metabolite. 25OHD circulates bound to vitamin D-binding protein (DBP) and has an elimination half-life of ~15 days. The second hydroxylation step occurs in the kidney and results in the formation of $1,25(OH)_2D$. Both 25OHD and $1,25(OH)_2D$ circulate bound to DBP; however, it is the free form of $1,25(OH)_2D$ that is regarded as the metabolically active hormone.[7] Toxicity from high circulating levels of 25OHD may therefore be due to either displacement of $1,25OH_2D$ from DBP by excess circulating 25OHD or, as has recently been demonstrated, 25OHD could directly bind to the vitamin D receptor to activate target genes involved in calcium haemostasis.[8] Previous animal investigations demonstrated that adipose tissue contains the greatest exchangeable pool of vitamin D_3.[9] Consequently, the reduced fat stores in our patient are likely to have resulted in a smaller volume of distribution and as a result higher serum levels of 25OHD.

The decline in 25OHD and consequently the elimination half-life was longer in our case than the previously published elimination half-life of ~2 months.[7] The decline in 25OHD reported by Araki *et al*. and in case two reported by Lowe *et al*. both showed a biphasic time course with a more rapid elimination time initially, then a subsequent slower elimination half-life of ~2 months.[1,2] This biphasic response could be consistent with an initial distribution equilibrium and subsequent steady-state elimination phase following a recent single, high-dose ingestion of vitamin D.

The frequency of hypervitaminosis D could increase in the future if higher target thresholds of treatment are advocated, the benefit of replacement is extended to non-musculoskeletal diseases and the availability of

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higher dose therapy increases. The minimum 25OHD target concentration recommended for supplementation remains debatable, with some experts advocating a threshold closer to 75 nmol/L (30 ng/mL) while other consensus documents advocate a threshold closer to 50 nmol/L (20 ng/mL).[10–12] The Australasian position statement on adult vitamin D and bone health recommends a vitamin D concentration ≥50 nmol/L at the end of winter or 10–20 nmol/L higher at the end of summer because seasonal variance is required for optimal bone health.[10] Standard cholecalciferol supplementation required to achieve these therapeutic targets is very unlikely to result in inadvertent 25OHD toxicity in healthy individuals.[13] There has been a dramatic increase in potential disease associations with vitamin D published over the last decade. While there is still debate over causality and benefit of high dose vitamin D supplementation, some practitioners advocate high doses of vitamin D. There are currently four compounding pharmacies providing high-dose (~50 000 IU) vitamin D preparations in Western Australia. Formulating preparations of medicines with doses that are not commercially available is a recognised role of the compounding pharmacist.[14] However, concerns have been raised over the level of regulation covering compounding. The Therapeutic Goods Administration in Australia is currently reviewing options for the regulation of pharmacy compounding.[15]

Our case illustrates several important points: hypervitaminosis D from unactivated vitamin D therapy usually requires very high doses of cholecalciferol, the suppression of PTH may not occur with unactivated vitamin D toxicity, especially in the presence of severe renal impairment and the acute kidney injury induced by hypercalcaemia from prolonged toxic ingestion of vitamin D may be partially reversible on cessation of vitamin D supplementation.

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