

VITAMIN D TOXICITY & UNDETECTABLE SERUM LEVELS – A CONUNDRUM

Vimal Venugopal, Miles J Levy, Narendra L Reddy, Faizanur Rahman and Ragini C Bhake

University Hospitals Leicester NHS Trust Kingdom

Presenting history

A 59 year old lady presented to the acute medical unit in May 2017 after being referred by her general practitioner for symptomatic hypercalcaemia. This had been picked up as part of monitoring bloods for an alternative medicine regimen.

She had a history of Multiple Sclerosis diagnosed in 1998, she had a relapsing remitting presentation initially and she was started on disease modifying therapy started on 2004, which she discontinued after a year partly due to needle phobia. She stopped having relapses but had problems with a gradual decline in mobility as well as spasms and urinary urgency. She was treated symptomatically by the local neurology service.

She had found an alternative medicine regimen – “The Coimbra Protocol”¹ -which is used to attempt to stop the progression of multiple sclerosis. This is a regimen which uses high doses of colecalciferol in combination with other supplements which include magnesium, Vitamin B2, Vitamin B5, omega 3 fatty acids. She had been consulting a nutritionist privately in Ireland who had been requesting regular blood tests as part of monitoring serum calcium levels and advising on dose adjustments. She had been advised to drink at least 3 litres of water a day.

She had started taking 10000 international units of colecalciferol daily since December 2016, her dosage had increased to 170000 IU once daily since March 2017.

In the 1 week leading up to her admission, she stated she had reduced her fluid intake to 2litres/day and had been feeling generally unwell.

Her blood test by her GP immediately prior to admission in May 2017 showed her serum calcium to be 3.66mmol/l (normal range 2.2-2.6mmol/l) and subsequently she was referred to hospital. All her previous calcium levels had been in the normal range. The initial blood test in hospital showed a serum calcium of 3.76mmol/l.

Medication	Dose
Colecalciferol	170000 IU once daily
Pre-activated Vitamin B2	6.4mg once daily
Omega 3 fatty acid supplements	3 tabs once daily
Magnesium Citrate	2 tabs once daily
Solifenacin	10mg once daily
Lactulose	10ml twice daily
Sennoside	7.5mg once daily

Medication history at time of presentation

Inpatient history

Parathyroid hormone level was checked at time of admission, result was 4.7pmol/l (normal range 1.6-7.5). Serum 25-hydroxy Vitamin D as measured by immunoassay (at our local laboratory) was reported as <15nmol/L which was not in keeping with history of ingestion of very high doses of colecalciferol.

In light of above results, myeloma screen and serum ACE (screening for sarcoidosis) were sent and returned negative. Computed tomography scans of her thorax, abdomen and pelvis was performed to investigate for a malignant aetiology, the only finding was that of an adrenal incidentaloma.

Treatment for the hypercalcaemia was with vigorous rehydration with intravenous 0.9% NaCl and stopping her vitamin D supplementation.

Her serum calcium had reduced to 2.64mmol/l six days post admission. Patient was discharged once all investigations above had been performed and patient was symptomatically better. She had expressed a wish to restart Vitamin D supplementation but she was asked not to restart Vitamin D supplementation until post discharge bloods showed that her calcium had normalised and her Vitamin D levels were coming down.

As the serum 25 hydroxy Vitamin D levels were not in keeping with history, bloods were sent off to a different laboratory.

Date	Adjusted calcium (mmol/l) NR (2.2-2.6)	Phosphate (mmol/l) NR (0.8-1.5)	Creatinine (micromol/l) NR (60-120)	Vitamin D (nmol/l)	PTH (pmol/l) NR (1.6-7.5)
27/04/2016	2.34	1.28	52	112	
03/02/2017	2.33	1.28	56	<15	4.1
08/05/2017	3.66	0.90	100		
09/05/2017	3.76	0.93	111	<15	4.7
10/5/2017	3.35	0.70	90		
11/5/2017	3.23	0.72	71		
13/5/2017	2.96	0.82	61		
15/5/2017	2.64	0.82	42		
02/06/2017				>374	
30/6/2017	2.52		47		

Post discharge of the patient, we received results from the external laboratory which gave a result of 862nmol/l (99.6% Vitamin D3). Thus the results from our local laboratory were looked at again, it emerged that the actual result was >374nmol/l, but an information technology (IT) error had actually caused the very high result to default to a <15nmol/l. As such extremely high vitamin D levels had not been seen before this IT error had not been picked up previously.

Discussion

Vitamin D toxicity can occur secondary to excessive supplementation of Colecalciferol or more commonly, its metabolites Calcitriol and Alfacalcidol. The toxicity presents as hypercalcaemia with characteristic symptoms such as nausea, vomiting, irritability and weakness.

Despite widespread use of colecalciferol supplementation, toxicity rarely occurs^{2,3}. Local guidelines to treat severe Vitamin D deficiency suggest a regimen of 10000 IU daily for two months and then 1000-2000 IU daily as maintenance. Public Health England guidelines⁴ suggest supplementation of 10 micrograms (400 IU) daily for all adults through Autumn and Winter, and supplementation of 400 IU all year round for at risk adults.

Thus in this case, it is important to note that the dosage of up to 170000 IU daily is far in excess of usual recommended dosages for treatment and prophylaxis of Vitamin D deficiency.

Interestingly the parathyroid hormone level was in the normal range despite the elevated serum calcium levels.

Reviewing the case reports of Vitamin D toxicity, a similar picture of non suppressed PTH (in the normal range) has been reported on multiple occasions^{5,6,7}. The normal PTH level in combination with the initial reported undetectable level of 25 hydroxy-Vitamin D led us to investigate other causes of hypercalcaemia.

Learning points

Although recommended dose of Vitamin D have not shown to cause toxicity, patients may be taking significantly higher doses than recommended in alternative medicine regimens and thus toxicity can occur with the use of colecalciferol over the counter supplements.

Parathyroid hormone can often be normal in the setting of Vitamin D3 toxicity, this maybe due to a slower rise in serum calcium than in other causes of hypercalcaemia.

When blood test results are not in keeping with the clinical picture, liaison with clinical chemistry teams can help clarify the situation especially in this case as a simple reporting error was the issue.

References:

1. The Coimbra Protocol - <https://www.coimbraprotocol.com/>
2. Changing Incidence of Serum 25-Hydroxyvitamin D Values Above 50 ng/mL: A 10-Year Population-Based Study. Dudenkov et al Mayo Clinic proceedings May 2015
3. Prevalence of hypercalcemia related to hypervitaminosis D in clinical practice. Perez-Barrios et al, Clinical Nutrition Dec 2016
4. Public health England Vitamin D supplementation guidelines - <https://www.gov.uk/government/news/phe-publishes-new-advice-on-vitamin-d>
5. Vitamin D intoxication: case report. Marins et al. Einstein (Sao Paulo) June 2014
6. Vitamin D intoxication caused hypercalcemia: Case report. Ugur et al. ECE 2017 Lisbon
7. Iatrogenic hypervitaminosis D as an unusual cause of persistent vomiting: a case report. Bansal et al. Journal of Medical Case Reports Feb 2014