

Hypervitaminosis-D, an Uncommon Reality!



Medical Science

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ABSTRACT

Vitamin D deficiency is highly prevalent in India. This has set off a trend amongst medical practitioners to prescribe vitamin D supplements empirically. Whilst this approach is generally safe, in predisposed individuals it may lead to hypervitaminosis D. Here we present a case where empirical use of high dose vitamin D supplementation had serious consequences highlighting the need to use vitamin D therapy judiciously and to remain vigilant for side-effects in high-risk individuals.

BACKGROUND

Nutritional deficiencies pose a significant health hazard worldwide especially in the developing world¹. Over the past decade a rise in the prevalence of vitamin D deficiency has further added to this burden in India². This is at least partly linked to the greater urbanisation and affluence in the society leading to reduction in exposure to sunlight².

Increasing recognition of the high prevalence of vitamin D deficiency in India has led to widespread use of vitamin D supplementation. The cost of establishing laboratory confirmation of vitamin D deficiency is high and as a result a significant proportion of vitamin D therapy is being prescribed empirically on clinical grounds exposing the population to the risk of vitamin D toxicity. Fortunately, significant vitamin D toxicity remains uncommon due to a wide gap between its therapeutic and toxic doses³, and reports of toxicity are rare even when higher doses are used.⁴ However older individuals and those with renal impairment or primary hyperparathyroidism (PHPT) could be predisposed to vitamin D toxicity³ and care needs to be taken while prescribing supplements to such individuals.

We present a patient in whom empirical high-dose vitamin D supplementation led to serious adverse consequences, raising concerns about its widespread use without prior risk assessment and appropriate clinical and biochemical monitoring during its use.

CASE

An eighty-nine year-old female family physician, who was professionally active and living independently, presented to an orthopaedic surgeon with a short history of bone aches and pains. The only significant past medical history was that of hypertension. She was clinically suspected to have vitamin D deficiency and was prescribed 3 intramuscular injections of 6 million units of cholecalciferol to be taken at monthly intervals.

A few days after the third dose she presented with nausea, generalised weakness, confusion and ataxia. Vital parameters were normal although she was mildly drowsy and dehydrated. Serum levels of calcium, phosphate, magnesium, creatinine and vitamin D at the time of presentation were as per table 1. Unfortunately parathyroid hormone level was not checked initially at the time of hospital admission. Abdominal ultrasonography showed normal sized kidneys but with altered corticomedullary differentiation, suggestive of renal parenchymal disease.

Table 1

	Reference Range	On admission	Post-treatment	Pre-discharge	6 weeks later
S. Calcium (mg/dl)	8.5 - 11	18.14	10.9	9.38	9.72
S. Phosphate (mg/dl)	2.5 - 4.5	4.6	4.5	4.2	4.1
S. Magnesium (mg/dl)	1.6 - 2.5	2.1	1.9	2.2	2.0
S. Creatinine (mg/dl)	0.5 - 1.5	4.49	2.34	2.33	1.29
eGFR (ml/min/1.73 m ²)	>90	10	21	21	41
PTH(pg/ml)	15 - 65	NOT DONE	62.9	58.1	4.7
S. Vitamin D3 (ng/dl)	54 - 90	>160	>160	>160	>160

Patient was commenced on normal saline infusion and intranasal calcitonin. In view of severe hypercalcemia and worsening oliguria and renal function, she underwent 2 sessions of hemodialysis which was complicated by disequilibrium syndrome. Over the next 5 days, she gradually recovered clinically with significant improvement in hypercalcemia and she was discharged. 6 weeks following discharge, she staged a full recovery and resumed her daily activities. Laboratory results during the hospital stay, pre-discharge and 6-weeks post discharge are also shown in table 1.

DISCUSSION

Vitamin D is an important pro-hormone which plays a vital role in bone and mineral metabolism and in maintaining normal function of muscle, immune system, cell differentiation and inflammation.⁵ Daily recommended allowance of vitamin D is 600 IU/day.⁶ Usual replacement dose in patients with established vitamin D deficiency is 1500-2000 IU/day of cholecalciferol⁷ and higher doses are often used in patients with severe deficit. As there is a significant gap between the usual replacement dose and possible toxic dose of >40000 IU/day⁸, vitamin D toxicity is rare but may result when high dose supplements are used over a short period of time.⁴

Hypervitaminosis D leads to exaggeration of vitamin D signal transduction process with accumulation of 25(OH) vitamin D and its active form 1,25 (OH)₂ vitamin D which in turn trigger gene expression in excess.³ These active metabolites of vitamin D stimulate calcium transport across intestine and distal tubules of kidney via actions on specific calcium channels TRPV6 (tran-

sient receptor potential cation channel subfamily V; member 6), calbindins and CaATPase. $1,25(\text{OH})_2$ vitamin D also stimulates osteoclastogenesis by inducing RANKL (receptor activator of NF-KB ligand).⁹Collectively all these actions lead to hypercalcemia.

Clinical presentation of hypervitaminosis D is quite varied and is mainly due to hypercalcemia and hyperphosphatemia as was seen in our patient who presented with nausea, vomiting, dehydration and acute renal failure.¹⁰ Prompt treatment with saline diuresis, bisphosphonates, calcitonin and glucocorticoids largely reverse the clinical and biochemical picture. In the absence of symptoms and significant hypercalcemia, an observational policy can be maintained following discontinuation of vitamin D supplements.

In India, clinicians often prescribe vitamin D supplements empirically and the main drivers for this are its high prevalence and the financial cost of investigations necessary to confirm the diagnosis. On most occasions replacement is in oral form and in modest doses. Occasionally large doses are prescribed risking the possibility of hypervitaminosis D. This adverse outcome is also more likely in high-risk individuals i.e. the elderly and those with renal failure or primary hyperparathyroidism (PHPT)⁴.

In our patient, associated primary hyperparathyroidism was excluded retrospectively by normal calcium and normal PTH during the follow up period. However she was elderly with some degree of pre-existing renal dysfunction and high dose of vitamin D was used. It is highly likely that these factors combined to lead to acute manifestations of vitamin D intoxication.

This case highlights the need for a pragmatic but safe approach while using empirical vitamin D supplements to avoid the uncommon scenario of serious adverse outcome. In India where

the prevalence of vitamin D deficiency is high and its laboratory confirmation is prohibitively expensive, empirical therapy clearly has its merits. However several measures can be adopted to reduce the risk of an adverse outcome. When empirical therapy is prescribed, use of high doses of vitamin D should be avoided especially in the elderly population. We would also recommend that prior to commencement of vitamin D therapy serum calcium and serum creatinine level should be routinely assessed to exclude PHPT and renal impairment respectively. In high risk situations or when the use of high dose is considered necessary, serum calcium should be monitored at regular intervals during the therapy. This approach is relatively inexpensive and would further reduce the risk of this uncommon complication of vitamin D therapy.

CONCLUSION

The case described above highlights the dangers of using empirical and unmonitored high dose vitamin D replacement therapy without periodic biochemical assessment especially in high-risk individuals. Hypervitaminosis D is uncommon but it can lead to critical illness and can be prevented by adopting a prudent approach described above.

KEY MESSAGE

- Vitamin D deficiency is widespread in India. Empirical use of modest doses in low-risk individuals is safe.
- Hypervitaminosis D is uncommon but can occur with unmonitored use of high dose vitamin D supplementation especially in high-risk patients.
- High dose supplementation should be avoided especially in the elderly, patients with renal failure or those with PHPT who are prone to develop vitamin D toxicity.
- During the use of vitamin D supplements these individuals should undergo periodic monitoring of serum calcium and serum creatinine levels at regular intervals.

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