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Vitamin D Toxicity in Adults: A Case Series from an Area with Endemic Hypovitaminosis D

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Abstract

Vitamin D deficiency state is endemic to the Kashmir valley of the Indian subcontinent. Physicians often treat patients with high doses of vitamin D for various ailments and on occasion the prescribed doses far exceed the requirements of the patients. Ten cases of hypercalcemia due to vitamin D intoxication are presented with features of vomiting, polyuria, polydipsia, encephalopathy and renal dysfunction. All the patients had demonstrable hypercalcemia and vitamin D levels were high in nine of the 10 cases. The patients had received high doses of vitamin D and no other cause of hypercalcemia was identified. Treatment of hypercalcemia resulted in clinical recovery in nine cases. We conclude that hypervitaminosis D must be considered in the differential diagnosis of patients with hypercalcemia in endemically vitamin D deficient areas. A careful history and appropriate biochemical investigation will unravel the diagnosis in most of the cases.

Introduction

Vitamin D is an important pro-hormone which, besides playing important roles in calcium homeostasis and bone mineral metabolism, is now recognized to subserve a wide range of fundamental biological functions in cell differentiation, inhibition of cell growth as well as immune modulation.[1] The daily requirement of vitamin D is about 200-600 units.[2] The skin produces 10,000 units of vitamin D after total body exposure to UV light. The current tolerable upper intake level in both Europe and North America is 50 ug/day (2000 iu/day)[3] but overwhelming bulk of clinical trial evidence indicates that prolonged intake of 10,000 units of vitamin D3 likely poses no risk. Because of this wide therapeutic index, vitamin D toxicity is extremely rare, but does occur at excessively high doses. Doses more than 50,000 IU/day raise levels of 25(OH) vit D to more than 150 ng/ml and are associated with hypercalcemia and hyperphosphatemia.[4] Vitamin D intoxication can be iatrogenic, due to self medication or accidental with over fortification of milk or contamination of common dietary constituents like table sugar or cooking oil.[5-9]

The Kashmir valley of the Indian subcontinent is situated at an altitude of 1574–5425 feet above the sea level at latitudes 320 20'–340 50' N and longitude 730 45'–750 35' E in the Northern mountainous regions of India. The valley is known to be vitamin deficient area with vitamin D deficiency seen in about 69.6% of individuals exposed to the outdoors and 100% of those confined indoors.[10] As such clinicians frequently treat patients with vitamin D for diverse clinical symptoms and these doses may at times be inappropriately high. We herewith present a case series of 10 patients seen over a 10-year period who had received high doses of vitamin D and presented with features of vitamin D overdose.

Case Series

Ten patients with various features of hypercalcemia due to vitamin D overdose were seen over a decade from 2000, and included 6 male and 4 female patients with ages ranging from 48 to 75 years (median: 61 years). The patients presented with clinical features of lassitude (n=3), vomiting (n=4), polyuria (n=5), poldispsia (n=5), altered sensorium (n=4), anorexia (n=3) and oliguria (n=5). Routine biochemical evaluation demonstrated hypercalcemia in all of the patients with serum calcium levels ranging from 12 to 13.98 mg/dl (mean levels 13.13 $\pm$ 0.79,normal 9-11 mg/dl) with corresponding phosphates ranging from 3.9 to 8.6 mg/dl (mean 5.36 $\pm$ 1.76 mg/dl, normal 3.5-5.0). All the patients had biochemical evidence of azotemia with serum creatinine levels ranging from 1.63 to 4.24 mg/dl (mean 2.96 $\pm$ 3.88, normal 0.8 to 1 mg/dl) and serum urea levels ranging from 54 to 109 mg/dl (mean 82.9 mg/dl, normal up to 38 mg/dl). Electrocardiograms of all the patients were normal. Eight of the 10 patients showed evidence of renal failure, whereas two patients had pre-renal azotemia. Serum vitamin D levels were elevated in nine cases (normal 70-144 nmmol/l) and serum parathormone (iPTH) levels were normal or low (normal 15-65 pg/ml) in the 7 patients in whom it was done, (Table 1). Nephrolithiasis was not demonstrable upon ultrasonography in any of the patients and all had normal sized kidneys with maintained corticomedullary differentiation. Serum and urine electrophoresis were normal in all cases. Causes of hypercalcemia such as multiple myeloma, granulomatous disease, intrinsic renal disease or hyperparathyroidism were ruled out

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in each case by appropriate clinical examination and relevant investigations including bone marrow examination (n=5) and radiological survey. All of the patients had a history of vitamin D ingestion in the form of multiple parenteral injections or weekly oral sachets of vitamin D for various indications that included low backache (n=4), radiculopathy (n=2), osteoarthritis (n=2) or generalized weakness (n=2). The dose of vitamin D ingested ranged from 3.6 million units to 210 million units over periods ranging from 1-4 months (median: 2). The patients were managed with saline diuresis (n=10), steroids (n=7), bisphosphonates (n=4) and calcitonin (n=1). Nine patients recovered from the symptoms with treatment and a demonstrable biochemical recovery of renal failure (n=7) and hypercalcemia (n=5). One patient expired due to multiorgan failure as a result of concomitant sepsis. The eight surviving patients were doing well on follow up lasting 6-12 (median: 9) months during which their vitamin D and calcium levels normalized; one patient was lost to follow up.

Table 1: Biochemical features in individual patients

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age	70	65	65	55	65	55	75	57	48	51
Vit D dose (x100,000 units)	210	108	?	?	120	?	540	30	?	600
Ca	13.5	12	13.9	12.35	12.6	12.4	13.98	13.6	12.9	14.2
Phosphates	8.6	7.5	5.6	-	3.9	4.3	-	4.5	4.5	4.0
i-pTH	15	41.75	3.1	-	-	4.7	-	18	29	3.1
25 (OH) Vit D	302	172	200	165	164	283	100	236	176	306
Urea (mg/dl)	87	88	100	51	99	109	70	104	54	67
Creatinine (mg/dl)	3.8	2.7	3.4	1.63	3.13	3.2	3.8	2	1.7	2.0
24 hr Urinary Phosphate (mg)	150	1500	100	-	-	-	-	-	-	160
24 hrs calcium (mg)	-	980	-	425	500	221	250	245	200	416

OA=Osteoarthritis, S/S=Signs/symptoms, RF renal failure, LBA=Low backache, 25(OH)Vit D = 25, hydroxyl vitamin D

Discussion

The highest chronic daily oral intake of vitamin D that will pose no risk of adverse effects for most healthy adults has not been elucidated.[11] The Food and Nutritional Board, USA evaluated the potential for high intakes of vitamin D to produce adverse effects and set a safe Tolerable Upper Intake Level (UL) of 50 µg (2000 IU) for vitamin D_3.[2] Subsequently, the European Commission Scientific Committee on Food (SCF) also identified a vitamin D_3 UL of 50 µg as a safe upper limit.[12] Since the synthesis of $1,25(OH)_2D_3$ is tightly regulated, extremely large doses of vitamin D, on the order of 100,000 units per day, are required to cause hypercalcemia.[1] The median lethal dose of vitamin D is 21 mg (8,40,000 IU) /kg and, which in overdose, affects all major organ systems.[13]

Patients present with nausea, vomiting, weakness, and altered level of consciousness. Polyuria, excessive thirst and other manifestations like painful periarticular calcinosis, nephrocalcinosis, hypertension, renal failure or band keratopathy and hearing loss have been reported.[1,14,15] The symptoms of vitamin D toxicity can stem from the deposition of calcium phosphate crystals in soft tissues throughout the body,[1] which can occur once the calcium-phosphate product is >60. Acute hypercalcemia directly shortens the myocardial action potential, which is reflected in a shortened QT interval.[16] Arrhythmias and ST segment elevations mimicking myocardial infarction have also been reported.[17,18]

The mechanism of vitamin D toxicity in hypervitaminosis D is postulated to be an overwhelming of the vitamin D signal transduction process, whereby the catabolic system involving the CYP24A1 is unable to keep up with the target cell levels of activated vitamin D metabolites.[19] Three major theories have been put forth by researchers about the mechanisms of vitamin D toxicity. All involve increased concentrations of a vitamin D metabolite reaching the vitamin D receptor in the nucleus of target cells and causing exaggerated gene expression. At issue, is the offending vitamin D metabolite and how it becomes elevated. The 3 hypotheses to explain this are as follows:[19]

1. Vitamin D intake raises plasma 1 alpha-$25(OH)_2D$ concentrations, which increase cellular 1-alpha $25(OH)_2D$ concentrations.
2. Vitamin D intake raises plasma 25(OH)D to concentrations that exceed the vitamin D binding protein, binding capacity and "free 25(OH)D" enters the cell, where it has direct effects on gene expression.
3. Vitamin D intake raises the concentrations of many vitamin D metabolites, especially vitamin D itself and 25(OH)D. These concentrations exceed the DBP binding capacity and cause release of "free" 1-alpha $25(OH)_2D$, which enters target cells.

Of the three hypotheses put forward to explain the triggering event of toxicity, increases in total 25(OH)D and free 1 alpha-$25(OH)_2D$ concentrations are the most plausible, although they remain unproven. However, even in the absence of definitive evidence to establish the responsible metabolite, the wealth of animal studies and human anecdotal reports of vitamin D intoxication indicate that plasma $25(OH)D_3$ is a good biomarker for toxicity.[19]

All of our patients except one had elevated vitamin D levels. Previously, an 85-year old female had been reported to develop hypercalcemia and other adverse side effects from a relatively low dose of vitamin D_3 (400 IU for 2 mo). The serum 25(OH) D concentrations on admission were 62 nmol/L, well below that believed to be associated with toxicity. However, serum 1,25 OH vitamin D levels were elevated.[20] Since we measured only 25(OH) vitamin D in our patients, it is possible that the 1,25(OH) vitamin D levels could have been higher in the patient with normal serum vitamin D levels and could have been responsible for the hypercalcemia seen in the patient. Normal or near normal levels of total 25(OH) vitamin D and $1,25(OH)_2$ vitamin D have been reported in patients with accidental exposure to a veterinary vitamin D concentrate and resultant hypercalcemia and its symptoms,[21] but serum free 1,25-dihydroxyvitamin D was elevated in all such patients. Free 1,25-dihydroxyvitamin D was not assayed in any of our patients.

Vitamin D intoxication is a treatable cause of hypercalcemia. Calcitriol-induced hypercalcemia usually lasts only one to two days due to the short biologic half-life of the compound.[22] Discontinuing the calcitriol, increasing salt and fluid intake or additional hydration with intravenous saline may be the only treatment needed. In contrast, hypercalcemia induced by intoxication with longer lasting preparations such as dihydrotachysterol, vitamin D_3 and vitamin D_2 takes longer to resolve because of deposition of ingested vitamin D in fat and its consequent slow release. Therefore, more aggressive therapy including intravenous hydration, diuretics and glucocorticoids is needed.[22] Since the hypercalcemia of vitamin D intoxication results from increased intestinal absorption of calcium and from the direct effect of $1,25(OH)_2D_3$ to increase resorption of bone in severe cases, therefore, bisphosphonate therapy can be usefully added to the therapeutic regimen of hydration and omission of dietary calcium.[23]

Our case series assumes importance in light of the fact that our patients belong to an endemically vitamin D deficient area; vitamin D deficiency being common in India despite abundant sunlight.[19-21] As such, it is common practice for medical practitioners to prescribe vitamin D preparations for nonspecific body, back and leg pains which are partly believed to be because of the deficiency state. Self medication with over the counter medications vitamin D preparations is also not uncommon and many a times multiple doses of the commercially available preparation of 600,000 units are administered, which has the potential to result in vitamin D toxicity.

Conclusion

Our study calls for careful dosing of vitamin D in such cases where it is believed to be of clinical use. Physicians also need to be wary of prescribing vitamin D in high doses without monitoring and must be sensitive to the potential toxic effects of a seemingly innocuous "vitamin." Pre treatment and follow-up vitamin D may need to be ordered for monitored evidence based treatment. Our data also emphasizes the consideration of vitamin D overdose in patients presenting with polyuria, poldispsia, vomiting, azotemia or encephalopathy in the emergency room. A careful enquiry into drug history and appropriate biochemical testing can unravel a treatable cause, generally considered rare in an area of florid vitamin D deficiency.

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