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Title: Vitamin D Intoxication in Three Children with Varied Manifestations: A Case Series And Review

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ABSTRACT

Introduction: Inadvertent and erroneous prescription of vitamin D beyond the recommended dosage and route of administration can cause vitamin D intoxication in children. Infants are particularly vulnerable to such toxicity. Clinical features are due to hypercalcemia, which range from mild to life threatening symptoms. Here we report two infants and one child who had varied manifestations due to hypercalcemia resulting from empirical treatment with high doses of vitamin D. We discuss the management strategies in these cases along with a brief review of literature.

Case report: Our first case was a ten month old infant who presented with fever, vomiting and failure to thrive. On detailed clinical examination and investigation revealed hypertension and bilateral nephrocalcinosis along with urinary tract infection. The second child was two year old and had severe hypercalcemia with clinical features mimicking acute bacterial meningitis. The third infant had mild symptoms like constipation and irritability, and investigations showed moderate hypercalcemia. All had a history of inappropriate administration of vitamin D, either in oral or parenteral form and they were all successfully treated by us.

Conclusion: This case series stresses the importance of proper dosage, avoidance of parenteral route, along with appropriate clinical and biochemical monitoring during the course, whenever a dose of vitamin D is advised.

KEY WORDS
Vitamin D, Hypercalcemia, Nephrocalcinosis, Infant, Child.
Introduction:
Vitamin D deficiency (VDD) is being recognized more frequently in India among children over the past decade, causing increased burden of health hazards and expenditure despite adequate sunshine in this sub-continent (1). Increasing awareness about high prevalence of VDD has caused widespread use of oral vitamin D supplements with occasional high parenteral doses, given empirically on clinical ground only. Infants often receive such treatment for nonspecific complaints like failure to thrive, delayed dentition, late walking and physiological genu valgus, resulting in vitamin D intoxication (VDI). The reasons for such practice are high laboratory cost and non-availability of the test widely (2). The increased calcium absorption from intestine and bone resorption due to Vitamin D overdose can cause hypercalcemia and hypercalciuria resulting in nephrocalcinosis, urolithiasis and other soft-tissue calcifications (3). Here we describe three children diagnosed to be cases of VDI with different manifestations, due to unsupervised administration of very high doses of Vitamin D over a prolonged period. This case series warns against indiscriminate use of mega dose of vitamin D in parenteral as well as oral form, by the practicing pediatricians.

Case presentations:

Case 1
A ten-month-old male infant with severe acute malnutrition (SAM) and delayed motor development was admitted with complaints of fever and vomiting for seven days and not growing well for last six months. He was exclusively breastfed up to four months of age. On physical examination he was febrile, pale with generalized muscle wasting and without any signs of dehydration. He had tachycardia (HR 120/minute) and found to be hypertensive (BP- >95th centile). The other systemic examination findings were unremarkable. He was clinically diagnosed as a case of SAM with probable sepsis and reno-vascular hypertension.
Laboratory investigations revealed microcytic hypochromic anemia, normal serum electrolytes and renal function tests (Table 1). Renal ultrasonography was done in view of the presence of hypertension, which showed bilateral grade 2 medullary nephrocalcinosis (NC) to our surprise (Figure-1) (4). Further biochemical test results showed severe hypercalcemia with normal phosphorus, low parathormone (PTH), very high serum 25(OH) D and hypercalciuria, suggestive of VDI. Liver function tests and serum amylase were within normal range. Radiograph of wrist with elbow, ECG and Echocardiography did not show any abnormality. Urine culture grew *citrobacter freundii*. On detailed enquiry it was revealed that the baby had received vitamin D in a cumulative dose of 7200,000 IU over three months (injection Vitamin D 600,000 IU weekly IM) prescribed by practicing physician on complaints of delayed sitting, poor weight gain and delayed dentition. He had no history of polyuria, constipation or pain abdomen.

He was treated with intravenous saline (150 ml/kg/day), oral furosemide (1 mg/kg/day) and oral nifedipine (0.25 mg/kg/day) along with antibiotics for urinary tract infection. Breast feeding was withheld temporarily and all medications containing vitamin D and calcium were stopped. During this treatment he was monitored regularly for improvements of symptoms, urine output and serum calcium level. Due to persistent hypercalcemia, oral alendronate was added in a dose of 5 mg/day after three days. The child responded to it and serum calcium dropped to 12 mg/dl. He required total three doses of oral alendronate before discharge, when serum calcium was 10.5 mg/dl. As the hypertension was controlled, we advised to continue with oral furosemide and asked for follow up. After 15 days the child was readmitted with polyuria and hypercalcemia. This time he was treated successfully with six dose of oral alendronate. Now after six months the baby is normotensive, normocalcemic but with persistent medullary nephrocalcinosis.
**Case 2:**

A two-year-old girl was admitted with complaints of fever for ten days, poor feeding, irritability, lethargy and head banging for last two days. On clinical examination she was found to be conscious but irritable, drowsy, febrile, normotensive with some dehydration. CNS examination showed doubtful meningeal signs and depressed deep tendon reflexes. Other systemic examination findings were normal.

The child was managed as a case of acute bacterial meningitis as per protocol. Arterial blood gas analysis revealed high ionised calcium (3.2 m mol/L) with normal pH and bicarbonate level. Serum calcium level was 31.9 mg/dl. Other biochemical test results were obtained, which are listed in table 1. Her urine culture grew E coli which was sensitive to Amikacin. Suspicious of the severe hypercalcemia, detailed medication history was sought. He is found to have received 1800,000 IU of vitamin D (600,000 I.U, I.M weekly for 3 weeks) before presentation, prescribed by a practicing physician for poor weight gain. She was diagnosed to be a case of iatrogenic VDI and started on aggressive fluid therapy (150 ml/kg/day) along with intravenous furosemide (2 mg/kg/day) in divided doses. Injection hydrocortisone (1mg/kg/day) was added and intranasal calcitonin spray was given in a dose 200 IU, twice daily, due to unavailability of parenteral form of calcitonin. After 48 hours, sensorium improved and child became afebrile. Serum calcium came down to 15.4 mg/dL with normal renal parameters. Intranasal calcitonin was stopped after six doses. But due to a rebound hypercalcemia, oral alendronate (5mg/day) was added to the regimen. It was continued for three days, which resulted in fall of serum calcium. At the time of discharge her serum calcium was 11.5 mg/dL. She was advised to continue oral alendronate for another seven days (alternate day) with regular follow up. After two weeks serum calcium was 9.8 mg/dL. She is on regular follow up for last one year and maintaining normocalcemia.
Case 3

An 11 month-old male baby, a known case of recurrent wheeze admitted with complaints of irritability, poor feeding and constipation for last 15 days. He was exclusively breast fed till six months of age with introduction of semisolid food and cow’s milk thereafter. He was on supplementation of a multivitamin drop at a dose of 0.5 ml daily (containing vitamin D 200 IU) along with vitamin D3 800 IU per day since 15 days of life. The cumulative dose of vitamin D thus received was approximately 300,000 IU till the time of presentation. Investigations revealed normal blood counts and electrolytes except hypercalcemia and a high vitamin D3 level (Table 1). A diagnosis of VDI was made and treated by removal of exogenous source, withholding breast feeding, calcium restricted diet, diuresis with normal saline (1.5 times) and oral furosemide. After 48 hours serum calcium levels came back to normal and he was discharged after three days.

Discussion and Review of literature:

For the purpose of this review, citations were identified through PubMed searches, limited to last 15 years using the keywords “vitamin D toxicity” OR “vitamin D intoxication” OR “vitamin D poisoning” AND “child” OR “infant” AND “nephrocalcinosis”. Additional articles were identified from the reference list of identified papers. Only relevant papers in English language were taken in to consideration.

The exact incidence of VDI is unclear due to lack of any systematic studies addressing this issue. There are reports of this toxicity in children both from developed and developing countries (5,6). Since the first description of VDI in an Indian infant in 2004, it has been reported across the country (6,7,8). As per the global consensus recommendations on prevention and management of nutritional rickets, vitamin D deficient children (0-18 years) should be treated with vitamin D2 or vitamin D3 2000 IU per day for at least 12 weeks along
with oral calcium 500 mg per day regardless of age and weight (9). In children suspected to have VDD, Indian Academy of Pediatrics (IAP) recommends daily intake of 2000 IU of vitamin D along with 500 mg of calcium in infants and 3000-6000 IU of vitamin D with 600-800 mg of calcium in children in the age group 1-18 years, for a period of 3 months (10). If larger doses are to be given, then 60,000 IU of vitamin D weekly for 6 weeks, preferably in oral form, is recommended. Intramuscular vitamin D should only be administered to children with rickets having severe mal-absorption.

The relationship between the amounts of vitamin D intake causing excess or toxicity and corresponding severity of hypercalcemia have not been well studied in paediatric age group. It has been found that intake of 50,000 units of vitamin D or more can result in its poisoning in a person having normal parathyroid function and vitamin D metabolism (11). Our first and second patient had received very high doses of vitamin D, intra muscularly, whereas the third child had taken it in oral form. Serum vitamin D3 or 25 (OH) D levels up to 100 ng/ml is considered as safe for both children and adults, whereas level above 150 ng/ml is usually associated with VDI (12), which is evident from first two cases. Though our third case had vitamin D3 level only 138 ng/ml, still he had symptomatic hypercalcemia. This can be explained by genetic polymorphism, which regulates the synthesis and metabolism of vitamin D, vitamin D binding protein and the severity of hypercalcemia. In a study from Iran, 15 children younger than 12 year presented to pediatric emergency department with history of ingestion of more than 1500 IU/day of vitamin D supplements. Mean ingested dose was 406,700.7 ± 227,400.1 IU. Only one child had hypercalcemia and eight had vitamin D level more than 100 ng/ml. This study concluded that acute vitamin D toxicity may be a benign condition in Iranian children due to high prevalence of vitamin D deficiency in them. (13)

In a study from Turkey, authors found 70% of their VDI patients have received multiple doses of vitamin D periodically due to wrong dose, most commonly prescribed for the nonspecific
complaints including delayed walking or tooth eruption, which was also found in our cases (14). Joshi retrospectively studied seven children (six female, one male), aged between 7.5-25 months with hypervitaminosis D, who had taken vit D (900,000-4000,000 IU) prescribed by medical practitioners for wrong indications like failure to thrive (6). The clinical features were constipation, loss of appetite, lethargy, polyuria and dehydration. Hypercalciuria was present in all cases, whereas nephrocalcinosis was seen in five children. Hypercalcemia usually present with non-specific symptoms like poor appetite, pain abdomen, vomiting, constipation, muscle weakness, bone pain, polyuria and dehydration. As evident from first two cases, VDI can be a differential diagnosis in children presenting with clinical features of sepsis or acute bacterial meningitis. Hence a detailed medication history can clinch the diagnosis in such cases. Furthermore, the first baby had hypertension at presentation, which was reported as an unusual manifestation of VDI in infants elsewhere. This can be explained by the renal pathology and vascular calcification (15). Nephrocalcinosis (NC) is a well-known complication of VDI, seen in 10-25% of cases due to the deposition of calcium salts in tubular cells of loop of henle and basement membrane epithelium (6,16). These are classically distributed along the cortico-medullary junction, which can be detected easily in USG than plain radiography or computed tomography (CT) (8, 17). In a Taiwan study, five out of 16 children (31%) with nephrocalcinosis had a history of vitamin D intoxication (18).

Hypercalcemia is classified according to serum calcium level as mild (<12mg/dL), moderate (12-14 mg/dL) and severe (>14 mg/dL) (16). Our first and second patient had severe hypercalcemia (14.8 mg/dL, 31.2 mg/dl) and very high 25(OH)D level (>150 ng/mL). To our knowledge hypercalcemia to the extent of 31.2 mg/dl had never been reported in literature in children with VDI. Severe hypercalcemia needs emergency intervention due to its widespread multisystem adverse effects including death, which demands rapid correction.
The treatment of VDI is mainly aimed at managing symptomatic hypercalcemia, which results from increased intestinal absorption of calcium and from the direct effect of 1,25 dihydroxy vitamin D to increase resorption of bone. There are no national or international guidelines available for management of VDI. Treatment options available in children currently include discontinuation of vitamin D intake, intravenous hydration with normal saline, furosemide, glucocorticoids, calcitonin, alendronate, pamidronate, and hemodialysis, mainly based on case reports and small studies (14).

Primary treatment of symptomatic hypercalcemia is aggressive fluid therapy with normal saline at 1.5-2.5 times maintenance along with loop diuretics to increase the urinary flow and calcium excretion (19). Corticosteroids and calcitonin can be added in non-responsive cases. Glucocorticoids decrease both intestinal absorption and renal reabsorption of calcium. However, the onset of action may take up to 3 days and they are less efficient in ‘severe hypercalcemia’ (9, 14). Due to inherent nephrocalcinosis and persistent hypertension, we did not recommend steroid in first case. Third case was managed with IV fluids and loop diuretics only, as it was thought to be mild variant. Calcitonin is a hormone which directly inhibits the osteoclast function. Though it has rapid effect on serum calcium, its therapeutic uses are limited due to tachyphylaxis and reports of anaphylactic shock. We used calcitonin in the form of nasal spray in the second child due to the presence of severe hypercalcemia. Biophosphonates can successfully control hypercalcemia by osteoclast apoptosis and also due to its anti-resorptive action on bone. We treated first two cases with oral alendronate successfully. Alendronate as a 1st line treatment for VDI in an infant was first described in 2003, where the patient required a total 30 mg to achieve normocalcemia (5). In a recent series, alendronate achieved normocalcemia four times faster than prednisolone including reduced hospital stay (20). But another study showed recurrence of hypercalcemia in children on follow up, who received only alendronate in addition to I.V fluid and loop diuretics (3 out of 11), as in our
first case (14). Though there are reports of resolution of NC by few authors, complete resolution may not be seen even after follow up of 1-13 years (21, 22). Our first patient had persistent NC at 6 month follow up. Due to long half-life of vitamin-D, regular monitoring of symptoms and serum calcium level in patients with VDI is highly recommended.

**Conclusion:**

Iatrogenic vitamin D toxicity is not uncommon in children due to its indiscriminate use and prescription of very high dosage particularly in parenteral form by the medical practitioners for nonspecific complaints. Infants and children with severe malnutrition are more susceptible to it. Before recommending mega doses of vitamin D, its deficiency should be confirmed by appropriate laboratory tests. Parents should always be explained regarding the adverse effects of such therapy and the importance of regular follow-up. In the current scenario, there is a dire need for creating awareness among practitioners against unsupervised empirical treatment for VDD in order to prevent such menace.
Table 1:

Haematological, biochemical and radiological findings of three children with vitamin D intoxication.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Case 1 (10 month)</th>
<th>Case 2 (2 year)</th>
<th>Case 3 (11 month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm/dL)</td>
<td>10.2 (10.5-14)</td>
<td>11.6 (11.5-14.5)</td>
<td>10.5 (10.5-14)</td>
</tr>
<tr>
<td>TLC (x 10^3/c mm)</td>
<td>12.3 (6-14)</td>
<td>18.89 (4-12)</td>
<td>10.5 (6-14)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>135 (134-144)</td>
<td>140 (134-143)</td>
<td>140 (134-144)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>5 (3.5-6.1)</td>
<td>3.9 (3.3-4.6)</td>
<td>3.9 (3.5-6.1)</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>98 (98-106)</td>
<td>102 (98-106)</td>
<td>96 (98-106)</td>
</tr>
<tr>
<td>Bicarbonate (meq/L)</td>
<td>22 (21-28)</td>
<td>23 (21-28)</td>
<td>24 (21-28)</td>
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<tr>
<td>Calcium (mg/dL)</td>
<td>14.8 (8.8-10.8)</td>
<td>31.9 (8.8-10.8)</td>
<td>12.2 (8.8-10.8)</td>
</tr>
<tr>
<td>Ionised calcium (mmol/L)</td>
<td>2.6 (1.12-1.23)</td>
<td>3.2 (1.12-1.23)</td>
<td>1.2 (1.12-1.23)</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.5 (3.8-6.5)</td>
<td>2.8 (3.8-6.5)</td>
<td>4.2 (3.8-6.5)</td>
</tr>
<tr>
<td>Magnesium (mg/dL)</td>
<td>2.5 (1.6-2.6)</td>
<td>1.9 (1.6-2.6)</td>
<td>2.4 (1.6-2.6)</td>
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<tr>
<td>AST (U/L)</td>
<td>42 (22-63)</td>
<td>56 (20-60)</td>
<td>48 (22-63)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>38 (12-45)</td>
<td>28 (5-45)</td>
<td>32 (12-45)</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>95 (82-283)</td>
<td>78 (104-345)</td>
<td>250 (82-283)</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>3.8 (1.9-4.9)</td>
<td>3.2 (3.4-4.2)</td>
<td>3.6 (1.9-4.9)</td>
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<tr>
<td>PTH (pg/ml)</td>
<td>4.84 (7-53)</td>
<td>2.8 (7-53)</td>
<td>5.2 (7-53)</td>
</tr>
<tr>
<td>25 (OH) D (ng/ml)</td>
<td>&gt;150 (25-80)</td>
<td>&gt;150 (25-80)</td>
<td>132 (25-80)</td>
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<tr>
<td>Urea (mg/dL)</td>
<td>38 (5-18)</td>
<td>46 (5-18)</td>
<td>32 (5-18)</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>0.32 (0.03-0.50)</td>
<td>0.48 (0.03-0.50)</td>
<td>0.25 (0.03-0.50)</td>
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<tr>
<td>Urine calcium creatinine ratio</td>
<td>2.33 (0.2-0.6)</td>
<td>0.8 (&lt;0.2)</td>
<td>1.2 (0.2-0.6)</td>
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<tr>
<td>CSF Cytology, Biochemical, C/S</td>
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<td>Normal, No growth</td>
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</tr>
<tr>
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<td>Result</td>
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</tr>
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<tr>
<td>ECG</td>
<td>Normal</td>
<td>QT interval shortening, ST elevation</td>
<td>Normal</td>
</tr>
<tr>
<td>Skeletal survey</td>
<td>Normal</td>
<td>Normal</td>
<td>Not done</td>
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<tr>
<td>Neuroimaging</td>
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<td>Normal</td>
<td>Not done</td>
</tr>
</tbody>
</table>

Hb, Hemoglobin; TLC, Total leucocyte count; AST, Aspartate transaminase; ALT, Alanine transaminase; PTH, Parathormone; 25(OH)D, 25 Hydroxy-cholecalciferol; CSF, Cerebrospinal fluid; ECG, Electrocardiogram.

*Age appropriate values are inside the parenthesis.

**Figure 1:**

Ultrasonography of both the kidneys (longitudinal view) showing diffuse echogenic pyramids (solid arrows) suggestive of nephrocalcinosis.
Ethical considerations:

Compliance with ethical guidelines:

The study was conducted as per the ethical guidelines of institutional ethics committee and informed consent was taken from the parents for publication of data.

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Author contributions:

All authors contributed in preparation of the manuscript.

Conflict of interest:

The authors declared no conflict of interest.
References:


