An Unsuspected Pharmacological Vitamin D Toxicity in a Child and its Brief Review of Literature

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ABSTRACT

Inordinate administration of Vitamin D beyond required doses and duration occurs as a sporadic event among frequent empirical therapies of pharmacological Vitamin D. Such instances lead to Vitamin D intoxication. Systemic hypertension is an unsuspected after-effect of Vitamin D toxicity in a child unlike other toxicity effects such as hypercalcemia, neurological deterioration, etc., Here, we report a case of a 1-year-old child who developed acute hypertension and severe hypercalcemia due to Vitamin D toxicity which was masked by initial dehydration such as illness and brief review of literature about clinical entity.

Key words: Vitamin D toxicity, hypercalcemia, hypertension, zoledronic acid

INTRODUCTION

Pharmacological Vitamin D is used to treat and prevent ricketic and related entities. Instances of inordinate administration of pharmacological Vitamin D or heavy use of dietary supplements happen and culminating in clinical or subclinical intoxication. Vitamin D intoxication induces hypercalcemic milieu and is associated with both immediate and late morbidities owing to long half-life of Vitamin D in serum and its deposition in fat tissues.[1] We report a child who developed acute hypertension, hypercalcemia, and electrocardiogram (ECG) alterations following prolonged nonprescription administration by mother. The case is reported here not only because of rarity of the clinical entity but also to highlight the need for proper monitoring of Vitamin D therapy, diagnosis, and treatment plan.

CASE REPORT

A 1-year-old male child presented to pediatric emergency with recent onset vomiting, lethargy, and poor appetite. On physical examination, the child was irritable, anxious, lethargic, slow skin pinch, and dry oral mucosa conforming to severe dehydration. The child was promptly started with regimen for severe dehydration correction.

But even after dehydration correction using intravenous fluids as prescribed in World Health Organization guidelines for dehydration management, the child continued to be irritable. Repeated blood pressure values were above 99th percentile against age, sex, and height-matched normal values suggesting acute hypertension. Furthermore, investigations revealed hypercalcemia (15.3 mg/dl) and marginally low serum phosphate levels. ECG depicted short QTc complex, wide and tall T-wave, and ST-segment elevation.

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depression in a normal sinus rhythm background. Serum parathyroid levels were marginally suppressed, thereby categorically excluding parathyroid hormone-mediated causes. There was first-degree increase in echogenicity of bilateral renal parenchyma on sonographic examination pointing nephrocalcinosis. It also excluded lymphoid mass lesion in abdomen. Renal function parameters and blood cell counts were normal.

On detailed scrutiny, mother revealed periodic administration of injections for alleged bow legs and calcium supplementation, once baby started standing and walking with support. And to compound the situation, baby was again prescribed with oral calcitriol 60,000 units on weekly basis after an upper respiratory tract injection 4 months back. Apparent rectification of bow legs inspired mother to procure and feed calcitriol sachets and calcium without prescription.

Hypercalcemia and hypertension were promptly colligated to Vitamin D overdose. Child was admitted in Intensive Care Unit, and instituted with intravenous hydration, loop diuretic (furosemide), prednisolone 2 mg/kg/24 h, calcitonin 5 units/kg, zoledronic acid 4 mg infusion single dose, and calcium channel blocker amlodipine. Calcitonin and zoledronic acid were discontinued after first-day therapy. Diet was changed to nonfortified one containing no Vitamin D and low in calcium.

ECG abnormalities started reverting toward normalcy along with serum calcium levels in next few days. High fluid intake, low calcium diet, prednisolone, and furosemide were continued for next 15 days. At the end of in-hospital treatment, serum calcium was normal, and blood pressure was below 95th percentile. The child was discharged with the recommendation of high fluid intake, low calcium diet, low doses calcium channel blocker, and a caution for danger signs.

**DISCUSSION**

Recent literature has grown exponentially regarding rampant clinical and subclinical Vitamin D deficiency and its adversities across all age groups. Such concerns have prudently led to its increased pharmacological use for the preventive and therapeutic purposes.\(^1\)\(^,\)\(^2\) Usually, therapeutic prescriptions for Vitamin D deficiency have two phases. Initial phase is to tackle acute deficiency state and revert altered metabolic state to normalcy. The second phase is to replenish body reserves. Prolonged therapeutic duration of this prohormone gives the vulnerability for clandestine toxicity.

The upper limit for long-term Vitamin D intake has been stated to be 1000 IU/day for patients <1-year and 2000 IU/day for older children.\(^1\)\(^,\)\(^2\) Toxic threshold doses have not been clearly identified for the pediatric population. Serum 25(OH)D concentrations as low as 140 ng/ml were found harmful. There may be varied individual response to a given dose owing to variations in the calcemic response to Vitamin D. Prolonged administration, poor age-matched dosages, and variable response to drug generate a broad overlap between therapeutic end and commencement of toxicity.\(^1\)\(^,\)\(^4\)\(^,\)\(^6\)

Suprathreshold levels of Vitamin D accentuate hypercalcemic response. Contrary to physiological actions of assisting mineralization via positive effect on intestinal absorption and proliferation of osteoblasts, high levels of 25(OH)D in serum upsurge osteoclastic activity. This leads to increased calcium resorption from bones and hypercalcemia. *In vivo* studies have postulated that 25(OH)D rather than 1,25(OH)\(_2\)D is responsible for toxicity by competitively binding with Vitamin D receptors.\(^4\)\(^,\)\(^7\)

Initial symptoms of Vitamin D intoxication are quite nonspecific such as loss of appetite, vomiting, constipation, growth retardation, and polyuria. Laboratory evaluation is needed to establish diagnosis. Suggestive laboratory findings are hypercalciuria, raised urinary calcium/creatinine ratio (normal <0.21, elevated serum 25(OH) Vitamin D levels (>140 ng/ml), and nephrocalcinosis.\(^1\)\(^,\)\(^8\)

Hypercalcemic milieu acts as foundation for calcific depositions in tissues, once calcium-phosphate product exceeds 60 mg/dl in blood and manifests clinically as nephrocalcinosis, vascular calcifications, nephrogenic diabetes insipidus, hypertension, and cardiac electrical abnormalities. Hypertension is composite outcome of renal pathologies and vascular calcifications. Vitamin D has half-life of approximately 8 weeks in adipose tissue and 15 days in circulation. Hypercalcemia may continue for few months until 25(OH) D levels return to normal.\(^6\)\(^,\)\(^9\)

Systemic hypertension is an uncommon manifestation of Vitamin D toxicity and can remain masked for long before exerting considerable effects on organ systems.

Treatment of Vitamin D toxicity is guided by clinical manifestations and severity of hypercalcemia. Patients with hypercalcemia >14 mg/dl (3.5 mmol/L) may not require immediate therapy except when there are manifestations of toxicity. These may be treated by removal of exogenous source, calcium restricted diet, and hydration-diuresis therapy. Serum calcium levels >14 mg/dl require aggressive therapy. Other than above-mentioned general measures, a regimen consisting of hydration-diuresis therapy, loop diuretics, and glucocorticoids should be instituted with the additional possibility of calcitonin and injectable bisphosphonates.
Loop diuretics promote calcium diuresis while glucocorticoids decrease the production of 1,25(OH)₂D and deter calcium absorption in renal tubules. Calcitonin and bisphosphonates have utility in severe cases. Calcitonin inhibits bone resorption and blocks release of calcium and phosphates in serum by action on osteoclasts. Parenteral bisphosphonates (zoledronic acid, pamidronate) are particularly useful in crisis situations and act by blocking osteoclast-mediated bone resorption. Hemodialysis shall be reserved for rebound hypercalcemia, medically unmanageable hypercalcemic crisis, and acute on chronic renal failure.[1-4,8,9]

Vitamin D toxicity-related cases seem to have iatrogenic component also. It is not uncommon but hugely prevalent practice to prescribe pharmaceutical Vitamin D to patients with loss of appetite, developmental delay, wide anterior fontanelle, delayed dentition, etc., with verbal dictation about purported use of particular drug. This has added to misuse of a beneficial drug among masses, as in our case. A humble effort to correctly diagnose and judicious treatment of deficiency disorders can prevent the sporadic instances drifting to intoxication.

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Conflicts of interest
There are no conflicts of interest.

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