

Vitamin D Toxicity in Young Breastfed Infants: Report of 2 Cases

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Introduction

Vitamin D toxicity in infants is not uncommon, and has been reported as early as the 1930s, usually due to antirachitic treatment with very high doses of vitamin D. This usually involves administration of 600 000 IU vitamin D₂ oral or intramuscularly (termed “stoss therapy”) resulting in vitamin D toxicity symptoms related to hypercalcemia.^{1–4} Most of these case reports occurred outside the United States.

Recently, there are reports of vitamin D toxicity in very young breastfed infants, mostly in the United States, from inadvertent overdose with highly concentrated vitamin D formulation obtained over-the-counter or from free-standing stores (Table 1).

There were also reports of toddlers that had vitamin D toxicity from over-the-counter (OTC) vitamin D overdose within the United States. They presented with symptoms of irritability, vomiting, constipation, and hypertension.^{9,10} The patients’ hypercalcemia resolved with standard treatments. One patient, a 16-month-old, had refractory hypercalcemia that was treated with pamidronate.¹⁰

Case Report

The 2 infants in this report have an identical presentation. One is a 3.5-month-old Caucasian female and the other a 2.5-month-old Caucasian male. They came to the emergency department, on separate occasions, for decreased feeding, lethargy, and inconsolable crying. Physical examination showed evidence of moderate dehydration. They are exclusively breastfed and have been receiving OTC vitamin D supplementation. Further questioning of the parents and later examination of the vitamin D bottles revealed that the infants received vitamin D supplementation way above the recommended dose, resulting in hypervitaminosis D and hypercalcemia (Table 2).

The infants received intravenous hydration with normal saline and dextrose-containing solution at 200% maintenance. They were admitted to the pediatric intensive care

unit (PICU) where they received furosemide 1 mg/kg/dose every 8 hours and prednisone 1 mg/kg/d. The second infant received calcitonin 4 IU/kg × 1 dose. They both had improvement of hypercalcemia after 2 to 3 days of treatment. On discharge, the first infant had a calcium of 11 mg/dL, and the second infant 10.8 mg/dL; both clinically improved, and tolerating feeding well. They were sent home on the low calcium, no vitamin D formula Calcilo XD. The first infant was readmitted to the PICU after developing symptoms of hypercalcemia because mom resumed breastfeeding even after being instructed not to. Her calcium level on readmission was 18 mg/dL. Nephrocalcinosis was noted on the first infant’s renal ultrasound, but not on the second infant. It took a few months for their 25(OH)D to normalize (Table 3).

Discussion

Vitamin D dietary supplements are either plant-derived ergocalciferol (vitamin D₂) or animal-derived cholecalciferol (vitamin D₃).^{11,12} Vitamin D is hydroxylated to 25-hydroxyvitamin D—25(OH)D—in the liver, a process driven by substrate availability.^{13,14} 25(OH)D binds to vitamin D binding protein (DBP), preventing their rapid clearance in the urine, and resulting in a half-life of 15 days in the circulation.¹⁵ 25(OH)D is transported to the kidney bound to DBP for 1- α -hydroxylation to 1,25(OH)₂D and 24-hydroxylation to 24,25-dihydroxyvitamin D [24,25(OH)₂D].¹⁶ 1,25(OH)₂D (calcitriol) is the active form of vitamin D, whereas 24,25(OH)₂D has limited physiologic activity.

The degree of vitamin D excess correlates with the 25(OH)D, which reflects vitamin D stores. 1,25(OH)₂D, on the other hand, may be increased or normal, because of its regulation by the suppressed parathyroid hormone

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Table 1. Case Reports of Breastfed Infants Who Had Vitamin D Toxicity.

Year	Case Description	Diet and Vitamin Supplement	Laboratory Values/Treatment
2015 ⁵	5.5 mo male—parental concerns of vitamin D overdosing, baby was fussy and constipated	Vitamin D3 400 IU/drop Dose the child received: 14 400 IU daily × 4 months (mom administered a dropper full or 1 mL)	25(OH)D >150 ng/mL (30-100) Outpatient treatment: discontinuation of vitamin D supplementation
2015 ⁶	4 mo female—failure to thrive, dehydration; 3-day history of emesis, diarrhea, lethargy, dehydration	Exclusive breastfeeding Over-the-counter vitamin D3 Brand: <i>Seeking Health, Liquid Vitamin D3</i> 2000 IU/drop Dose the child received: 50 000 IU daily × 2 months (mom administered a dropper full)	25(OH)D 294 ng/mL (30-100) 1,25(OH) ₂ D 138 pg/mL (22-84) Ca 18.7 mg/dL (9-11) Parathyroid hormone <6 pg/mL (15-65) Inpatient treatment: fluids, calcitonin, and bisphosphonates
2014 ⁷	1.5 mo female—normal physical findings	Exclusive breastfeeding Vitamin D3 (<i>Vigantol oil Merck KGaA</i>) 10 drops daily, total of 200 000 IU per month	25(OH)D ₃ >400 nmol/L (50-125) Ca 2.72 mmol/L (2.2-2.7) Parathyroid hormone 6.6 pg/mL (10-69) Inpatient treatment: fluids, prednisolone, phenobarbital, and furosemide
2013 ⁸	3 mo male—asymptomatic, parental concerns of vitamin D overdosing, slightly increased patellar deep tendon reflexes on examination	Exclusive breastfeeding Over-the-counter vitamin D3 <i>Vitamin D preparation from a free-standing vitamin store</i> 400 IU/drop Dose: 12 000 IU daily × 20 days (mom had given 1 mL)	25(OH)D ₃ 422 ng/mL (30-100) 1,25(OH) ₂ D 61 pg/mL (27-71) Ca 10.5 mg/dL (8.8-10.8) Parathyroid hormone <3 pg/mL (15-65) Outpatient treatment: discontinuation of vitamin D supplementation

(PTH) and increased calcium, among others.¹⁷ Based on the patients described here and the review of literature, the patients presenting with symptoms of overt vitamin D toxicity usually have increased 1,25(OH)₂D.

Hypercalcemia is mediated by increased intestinal calcium absorption from increased free 1,25(OH)₂D.¹⁸ The excessive calcium load that is filtered through the kidney leads to hypercalciuria, because increases in plasma calcium is directly related to increase in urinary calcium.¹⁹ Hypercalciuria also results from inhibition of calcium reabsorption in the distal tubule due to the suppressed PTH.^{20,21} Elevated serum calcium, if prolonged, may cause polyuria, because of a decrease in the urinary concentrating ability. The mechanism behind this reduction in urine concentration is thought to involve excessive calcium acting via calcium-sensing receptors to reduce the antidiuretic hormone-stimulated water permeability of the collecting ducts, which may involve a decrease in aquaporin-2 water channels. This is thought to be a compensatory mechanism against renal stone formation during hypercalciuria.^{19,22}

The signs and symptoms of vitamin D toxicity in an infant may be nonspecific and subtle in the beginning. The symptoms are direct effects of hypercalcemia, and frequently correlate with the calcium level.²³ These include poor feeding, feeding intolerance, constipation, polyuria, dehydration, lethargy, irritability, failure to thrive, emesis and diarrhea.^{2,6} Because of the

vasoconstrictive effect of calcium, the patient may have hypertension.⁴ Hypercalcemia also leads to hypercalciuria and the complications of nephrocalcinosis and nephrolithiasis.^{1,9}

Differential diagnoses include Williams syndrome (7q11 deletion, which has infantile hypercalcemia as one of the features in 15% of patients,²⁴ “elfin facies,” and supravalvular aortic stenosis), and subcutaneous fat necrosis (which causes purple-bluish hard nodules and hypercalcemia from increased prostaglandin activity, release of calcium from necrotic fat tissue, and increased secretion of 1,25-dihydroxyvitamin D₃ from subcutaneous lesions, leading to an increased intestinal uptake of calcium²⁵).

Further evaluation include testing for total and ionized calcium, phosphate, alkaline phosphatase, PTH, 25(OH)D, and 1,25(OH)₂D. Finally, measurement of serum 24,25(OH)₂D and genetic studies for 24-hydroxylase (*CYP24A1*) gene, to evaluate for *CYP24A1* mutation leading to decreased metabolism of 1,25(OH)₂D, may be obtained.^{3,6} Findings of increased 25(OH)D, normal or increased 1,25(OH)₂D and suppressed PTH confirm the diagnosis of vitamin D toxicity.

Treatment is directed to ameliorate the infant’s dehydration and to acutely decrease the hypercalcemia. Infusion of 0.9% sodium chloride (10-20 mL/kg) to expand the extracellular compartment help decrease calcium levels, along with furosemide (1-2 mg/kg)-induced

Table 2. Clinical Features.

Age and Sex	Signs and Symptoms	Vitamin D Supplement	Laboratory Values
3.5-month-old female	<ul style="list-style-type: none"> Decreased feeding, lethargy, inconsolable crying for 1.5 weeks. 1-lb weight loss over 2 weeks Physical examination: pallor, dry lips, sunken fontanelles, sunken eyeballs, and hypertension 	<i>Whole Foods</i> vitamin D ₃ 2000 IU/mL, 1 mL daily for 2.5 months	<ul style="list-style-type: none"> Serum Ca 21 mg/dL (8.8-11.2) 25(OH)D 644 ng/mL Parathyroid hormone <1 pg/mL (14-72)
2.5-month-old male	<ul style="list-style-type: none"> decreased feeding, lethargy, inconsolable crying, vomiting after feeding for 2 days. physical examination: dry lips and sunken fontanelles 	<i>Emulsi-D3</i> (prescribed by chiropractor) vitamin D ₃ 2000 IU per drop, given 1 mL instead of 1 drop—about 20 000 IU daily for 1.5 weeks	<ul style="list-style-type: none"> Serum Ca 15 mg/dL (8.5-10.1) Ionized calcium 1.93 mmol/L (1.2-1.48) 25(OH)D 680 ng/mL 1,25(OH)₂D 166 pg/mL (15-75) Parathyroid hormone <7 pg/mL (15-65)

Table 3. The Decline in the Patients' Vitamin D Level Reflects the 15-Day Half-Life of 25(OH)D.

	Labs	Admission	2.5 Weeks	3.5 Months	8 Months
Case 1	25(OH)D ng/mL	680	288	24.9	38.1
	1,25(OH) ₂ D pg/mL	166	>190	327	48.8
	Labs	Admission	6 Weeks	2.5 Months	3 Months
Case 2	25(OH)D ng/mL	644	106	50.6	30.6
	1,25(OH) ₂ D pg/mL		109		

diuresis, by increasing calcium urinary excretion. Adequate urine flow must be established before adding diuretics to the management. The calcium may continue to rise despite these treatments because the tremendously increased 25(OH)D and 1,25(OH)₂D continue to drive intestinal calcium absorption even during treatment. The addition of prednisone (0.1-1 mg/kg/d), which reduces intestinal calcium absorption by decreasing 1- α -hydroxylation of 25(OH)D to 1,25(OH)₂D in the kidney, is very effective in lowering the calcium levels. Salmon calcitonin (4-8 IU/kg, subcutaneous/intramuscular) may lower calcium by inhibiting calcium mobilization from bone. Bisphosphonates—oral etidronate (5 mg/kg twice a day) and intravenous pamidronate (0.5-2 mg/kg)—have been used in infants with hypercalcemia due to vitamin D intoxication and subcutaneous fat necrosis. They lower calcium by adsorbing to the surface of hydroxyapatite crystals in bone and inhibit osteoclast function and bone resorption.^{1,10}

There is a resurgence of breastfeeding rates in the United States since the early 1970s, with health professionals becoming more involved in the promotion of breastfeeding.^{26,27} With this breastfeeding resurgence is

the reemergence of nutritional rickets in the United States.^{28,29} Rickets, a disease believed to be long gone,³⁰ is again described in the past 2 decades especially in breastfed dark-skinned infants.²⁸⁻³⁰ Breastfeeding as the sole source of nutrition, inadequate exposure to sunlight, and inadequate vitamin D supplementation are the identified risk factors.³¹

The reemergence of nutritional rickets prompted different institutions to create recommendations on vitamin D supplementation in breastfed infants, but there is a considerable lack of consensus among these recommendations.³²

The American Academy of Pediatrics, Institute of Medicine, Pediatric Endocrine Society, and Endocrine Society recommend that all infants less than 1 year old should have a minimum intake of 400 IU of vitamin D per day beginning soon after birth.^{11,12,14,33} This reflects adequate intake reference value rather than recommended dietary allowance (RDA), as RDAs have not been established for infants.¹² Breast milk has an average vitamin D content of ~22 IU/L (range: 15-50 IU/L) in a vitamin D-sufficient mother.³⁴ An infant usually receives less than 1 L of milk daily, which means an exclusively or partially breastfed infant receives less than 22 IU/d, way

Table 4. Comparison of Vitamin D Supplementation Recommendation Among Different Institutions.

Age	AAP, PES, IOM, Endocrine Society		Endocrine Society Recommendations for Patients at Risk for Vitamin D Deficiency		EFSA		Canadian Pediatric Society	
	RDA (IU/d)	UL ^a (IU/d)	RDA (IU/d)	UL ^a (IU/d)	RDA (IU/d)	UL (IU/d)	RDA (IU/d)	UL (IU/d)
0-6 mo	400 ^b	1000	400-1000	2000	None		400-800 ^c	
6-12 mo	400 ^b	1500	400-1000	2000	400 (7-11 mo)		400-800 ^c	
1-3 y	600	2500	600-1000	4000	600			
4-8 y	600	3000	600-1000	4000	600			
9-13 y	600	4000	600-1000	4000	600			
14-18 y	600	4000	600-1000	4000	600			

Abbreviations: AAP, American Academy of Pediatrics; IOM, Institute of Medicine; PES, Pediatric Endocrine Society; EFSA, European Food Safety Authority.

^aUpper limit (UL) is the maximum level above which there is risk of hypercalcemia.

^bIndicates adequate intake rather than recommended dietary allowance (RDA). There are no established RDAs for infants.

^cHigher RDA of 800 IU for northern Native communities during the winter months.

below the recommended 400 IU daily of vitamin D, thus requiring supplementation until the infant is taking at least 1 L of vitamin D–fortified milk per day. The upper limit intake (the level above which there is risk of adverse events¹²) for vitamin D supplementation is 1000 IU/d for infants 0 to 6 months and 1500 IU/d for infants 6 to 12 months. For patients at risk for vitamin D deficiency, the Endocrine Society recommends a higher upper limit of intake, 2000 IU/d. Our patients received prolonged vitamin D supplementation at or above the upper limit of intake (2000 and 20 000 IU/d). The patients' 25(OH)D were 6 times the upper limit of normal, resulting in severe hypercalcemia, even on the patient who was supposed to have received the upper limit of intake for patients at risk for vitamin D deficiency (2000 IU/d). Although there may be confounding factors affecting vitamin D metabolism in this particular patient, such as defects in 24-hydroxylation resulting in decreased clearance of 1,25(OH)₂D, it is worth reassessing the recommendations for the sake of patient safety (Table 4).

The PES defines vitamin D excess as 25(OH)D >100 ng/mL, an arbitrary designation considered to be the level at which one is at risk for vitamin D intoxication.¹¹ The Institute of Medicine expresses concerns about risks at 25(OH)D levels >50 ng/mL.³³ The Endocrine Society defines vitamin D intoxication as 25(OH)D exceeding 150 ng/mL.¹⁴ 25(OH)D levels >150 ng/mL are associated with hypercalcemia.³⁵

Limitations

The concentration of vitamin D supplements were not confirmed in the laboratory. The patients were not evaluated for genetic polymorphism in vitamin D metabolism, such as testing for defects in 24-hydroxylation, which

leads to decreased degradation of 1,25(OH)₂D and hypercalcemia.³²

Conclusions

The worst reported cases of vitamin D toxicity in breastfed infants were described here. With the promotion of breastfeeding and vitamin D supplementation, more and more cases of vitamin D toxicity are being reported; therefore, efforts at its prevention need to be enhanced. Providing written instructions on vitamin D supplementation, including start schedule, brand name, concentration, and dose is recommended. Recommending only brands with vitamin D concentration of 400 IU/mL (such as D-visol, Tri-visol, or Poly-visol), and warning against highly concentrated vitamin D preparations from free-standing stores may help avoid dosing mistakes. Medication reconciliation with particular attention to vitamin D concentration and dose at the 2- and 4-month visit with the pediatrician may help identify early vitamin D toxicity. 25(OH)D may be obtained if there is suspicion for hypervitaminosis D but is not recommended for routine screening.

Declaration of Conflicting Interests

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