Hypercalcemia in Children Receiving Pharmacologic Doses of Vitamin D

abstract

Vitamin D deficiency causes rickets, requiring vitamin D at doses greater than daily dietary intake. Several treatment regimens are found in the literature, with wide dosing ranges, inconsistent monitoring schedules, and lack of age-specific guidelines. We describe 3 children, ages 2 weeks to 2 and 9/12 years, who recently presented to our institution with hypercalcemia and hypervitaminosis D (25-hydroxyvitamin D levels >75 ng/mL), associated with treatment of documented or suspected vitamin D-deficient rickets. The doses of vitamin D used were within accepted guidelines and believed to be safe. The patients required between 6 weeks and 6 months to correct the elevated serum calcium, with time to resolution of hypercalcemia related to age and peak serum calcium, but not to peak 25-hydroxyvitamin D level. With recent widespread use of vitamin D in larger dosages in the general population, we provide evidence that care must be taken when using pharmacologic dosing in small children. With limited dosing guidelines available on a per weight basis, the administration of dosages to infants that are often used in older children and adults has toxic potential, requiring a cautious approach in dose selection and careful follow-up. Dosage recommendations may need to be reassessed, in particular, where follow-up and monitoring may be compromised. *Pediatrics* 2012;129:e1060–e1063

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KEY WORDS

hypervitaminosis D, hypercalcemia, rickets

ABBREVIATIONS

$1,25(OH)_2D$—1,25-dihydroxyvitamin D
25-OHD—25-hydroxyvitamin D
RDA—Recommended Dietary Allowance

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Pharmacologic dosages of vitamin D are used to treat infants and children with vitamin D deficiency rickets or hypocalcemia. One suggested treatment regimen for symptomatic vitamin D deficiency in children recommends 3000 to 15 000 IU daily for 4 to 6 weeks.[1] Others suggest dosing by age: 1000 IU/day for infants <1 month old, 1000 to 5000 IU/day for 1- to 12-month-old infants, and >5000 IU/day for children >12 months old.[2] With radiographic evidence of healing rickets, the dose may be reduced, but the suggested duration of pharmacologic dosing is as long as 2 to 3 months. Timely biochemical monitoring is critical in avoiding hypercalcemia, and most guidelines suggest documenting markers of a therapeutic response after 1 month of treatment.

We describe mild hypercalcemia in 3 children in whom vitamin D therapy was prescribed for suspected nutritional vitamin D deficiency. These cases raise the concern that even recommended treatment doses have potential for toxicity, especially if administered inappropriately, or for too long a period of time without biochemical monitoring. Recommended dose ranges have limited data to support their use and may exceed upper tolerable limits for infants and children.

CASE REPORTS

Case 1

This infant girl was born at 37.5 weeks of gestation to a 34-year-old mother via emergent cesarean delivery for maternal preeclampsia. There was no maternal history of diabetes, excessive alcohol use or smoking, but a limited dietary intake of dairy products. She self-administered prenatal vitamins, but received no other medications. Review of the mother's medical record revealed hypocalcemia, elevated serum alkaline phosphatase activity, increased hepatic transaminases, and an elevated intact serum PTH level (77 pg/mL, normal 10-65). An older sibling was healthy, and the family had no history of musculoskeletal disorders.

Craniotabes was noted on the first day of life. Weight and length were at the fifth and 28th centiles, respectively. No dysmorphic features or bone deformities were evident, and the results of the remainder of the physical examination were normal. Radiographs suggested decreased calvarial ossification, but a comprehensive skeletal survey was otherwise unremarkable. The total serum calcium level at birth was appropriate for the first 36 hours of life (8.2 mg/dL), and increased to typical levels by day 3 (Table 1). Serum 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) level was 74 pg/mL (normal for age); a 25-hydroxyvitamin D (25-OHD) level was not obtained. On day 7, she received a single 1000-IU oral dose of vitamin D_3. At 2 weeks of age, the serum 25-OHD level was 21 ng/mL, and she was assumed to have inadequate vitamin D stores. Thus, she was prescribed 1000 IU/day of vitamin D_3, in addition to a multivitamin (Tri-vi-sol, supplying 400 IU of vitamin D_3 per day) providing a total of 1400 IU of supplemental vitamin D daily. The mother continued to breastfeed and was supplemented with 400 IU/day of vitamin D_2.

After 2 months of this regimen (1400 IU of vitamin D per day), serum calcium (10.7 mg/dL) and 25-OHD (84 ng/mL) levels were elevated (Table 1). The 1000 IU vitamin D_3 supplement was discontinued, although Tri-vi-sol was continued, providing 400 IU of vitamin D_3 per day. The infant remained healthy, with length at the 50th centile, and weight at the 10th centile. At 5 months, serum calcium and 25-OHD levels remained elevated and mild hypercalciuria was evident (Table 1). Thus, the multivitamin was discontinued, and additional oral hydration was begun.

By 6 months of age her biochemistry values had normalized. Radiographs demonstrated improved cranial mineralization. She has not required additional therapies and remains well without vitamin D supplementation.

Case 2

This 4-month-old African American boy presented during the winter with a seizure. He was an otherwise healthy 7-kg infant, with no pre- or postnatal complications. He met developmental milestones appropriately, received no medications, and had no known allergies. He was exclusively breastfed, without vitamin D supplementation. His mother had received no supplemental vitamins or mineral supplements for the previous 2 to 3 months. Physical examination results were unremarkable, with no dysmorphic features or abnormal neurologic findings.

TABLE 1 Biochemical Values in Case 1 Before, During, and After Vitamin D Treatment

	Before Vitamin D		During and After Vitamin D							
Age	1 d	3 d	12 d	2 mo	3 mo	5 mo	6 mo	7.5 mo	10 mo	24 mo
Vitamin D (IU/day)	—	—	1400	1400	400	400	0[a]	0	0	0
Calcium	8.2	9.3	—	10.7	10.2	11.0	10.2	11	10.5	9.9
Phosphorous	5.0	7.6	—	6.5	7	5.9	5.6	5.8	4.7	4.2
ALP (U/L)	—	—	265	429	393	—	265	—	—	256
iPTH	—	—	—	11	—	<3	—	—	—	—
25-OHD	—	—	21	84	69	78	65	55	58	33
$1,25(OH)_2D$	74	—	—	88	79	56	59	—	41	57
Urine Ca/Cr ratio	—	—	—	—	—	1.14	0.1	0.34	0.31	0.3

Reference values are as follows: calcium (8.8–10.2 mg/dL), phosphorous (2.2–4.2 mg/dL), iPTH (10–65 pg/mL), 25-OHD (>20 ng/mL) $1,25(OH)_2D$ (15–75 pg/mL), urine calcium to creatinine ratio (mg/mg) (normal for age <0.8). To convert from mg/dL to mmol/L: for calcium, multiply by 0.25; phosphorous, multiply by 0.323. To convert 25-OHD from ng/mL to nmol/L multiply by 2.5. To convert $1,25(OH)_2D$ from pg/mL to pmol/mL multiply by 2.6. ALP, alkaline phosphatase activity; iPTH, intact parathyroid hormone; Ca, calcium; Cr, creatinine.

[a] Patient continued to receive ~500 IU/day of vitamin D through dietary intake from 6 mo through follow-up.

Initial biochemical evaluation revealed hypocalcemia (5.5 mg/dL) and vitamin D deficiency (Table 2). Electrocardiogram revealed prolonged QT waves. Rickets of the distal radius and ulna was evident on radiographs. He was initially treated with intravenous calcium gluconate, and subsequently with oral ergocalciferol (4000 IU/day), calcitriol (0.5 μg/day), and calcium carbonate (100 mg/kg per day of elemental calcium).

One week after hospital discharge, serum calcium (10.3 mg/dL) and 25-OHD (33 ng/mL) concentrations normalized. Thus, his ergocalciferol dose was decreased to 2000 IU daily, calcitriol was discontinued, and calcium supplementation was reduced to 50 mg/kg per day. Six weeks later, a mild elevation in serum calcium persisted (10.4 mg/dL), 25-OHD had increased (79 ng/mL), and mild hypercalciuria was evident (random urine calcium/creatinine ratio, 0.9 mg/mg, normal <0.8 mg/mg). All calcium and vitamin D supplementations were discontinued. Six weeks later, serum calcium normalized (10.1 mg/dL), and there was a significant reduction in the 25-OHD level (40 ng/mL).

Case 3

This 2 9/12-year-old African American girl was exclusively breastfed until 5 months of age. A multivitamin providing 400 IU of vitamin D daily was prescribed during the newborn period, but compliance with this regimen appeared limited. At a 2-year well-child examination, mild tibial bowing was observed. She remained primarily breastfed with supplemental table foods. There had been no previous hospitalizations or major illnesses, and no use of medications. Biochemical evidence of vitamin D deficiency was documented (Table 2), and rickets was evident on lower extremity radiographs. She was provided 2000 IU of vitamin D daily with Tri-vi-sol (containing 400 IU/day of vitamin D_3) and ergocalciferol (1600 IU/day). Three months later, hypercalcemia (10.9 mg/dL) and hypervitaminosis D (25-OHD 102 ng/mL) were evident, and vitamin D supplementation was discontinued. After 3 months off vitamin D therapy, serum calcium (9.9 mg/dL) concentration normalized, and the 25-OHD level decreased to 24 ng/mL. At this time, Tri-Vi-Sol was resumed with the goal of providing 600 IU of vitamin D per day, the Institute of Medicine's recently revised Recommended Dietary Allowance (RDA) for this age group.[3]

TABLE 2 Clinical Summary

	Case 1	Case 2	Case 3
Age at initiation of treatment	2 wk	4 mo	2 and 9/12 y
Vitamin D dose, IU	1400/d × 2 mo 400/d × 3 mo	4000/d × 1 wk, 2000/d × 6 wk	2000/d
Duration of treatment, wk	8	7	12
Total vitamin D load, IU	120 000	112 000	168 000
Clinician indication for treatment	Craniotabes	Hypocalcemic seizures	Tibial bowing
Initial biochemistry values			
Calcium, mg/dL	9.3	5.5	9.9
Ionized calcium, mg/dL	—	2.2	—
Phosphorus, mg/dL	7.6	6.4	4.9
Alkaline phosphatase activity, U/L	265	1110	661
Midmolecule PTH, nlEq/mL[a]	—	58	—
Intact PTH, pg/mL	—	—	102
25-OHD, ng/mL	21[b]	<5[c]	5[d]
$1,25(OH)_2D$, pg/mL	74	7	156
Peak calcium, mg/dL	11	10.4	10.9
Peak 25-OHD, ng/dL	84	102	79
Peak $1,25(OH)_2D$, pg/mL	88	Not obtained	165
Time to resolution of hypervitaminosis	6 mo	6 wk	3 mo

PTH, parathyroid hormone.

[a] Reference ranges: Midmolecule PTH <25; intact PTH10–69 pg/mL.

[b] Measured at Esoterix Laboratories, Calabasas, California, by using high-performance liquid chromatography tandem mass spectrometry; reference range for all ages, 32–100 ng/mL.

[c] Measured by using radioimmunoassay kit methodology (DiaSorin, Stillwater, Minnesota), reference range reported as >20 ng/mL.

[d] Measured at Quest Diagnostics, by using liquid chromatography tandem mass spectrometry. Reference range reported as 30–100 ng/mL.

DISCUSSION

Recent concerns regarding vitamin D deficiency in young children, with a high prevalence in African American, breastfed infants in northern latitudes[4] has led to increased pharmacologic vitamin D therapy in this age group. Although vitamin D dosing schedules in this setting are available,[1,2] their safety may depend on the severity of disease or deficiency, and duration of therapy. Because there are individual variations in the calcemic response to vitamin D, there may well be a wide range of responses to a given dose.[5] This variance is likely due to differences in absorption, metabolism, concentration of vitamin D-binding protein in serum, and the capacity of storage sites.[5]

Furthermore, there is a lack of weight-based analyses of vitamin D dosing and kinetics; historically, RDAs have been equivalent across much of childhood and adult age ranges, despite large differences in body mass. Risk for toxicity for many agents increases with higher per body weight dosing, and the absolute doses determined in adults are likely unsafe for children. The cases described herein suggest that the time to resolution of hypervitaminosis D and hypercalcemia vary by age and peak serum calcium, but not by peak 25-OHD level (Table 2).

In addition to the aforementioned cases, we recently encountered a fourth child

who was given high doses of vitamin D for an inappropriate indication, and not monitored by a physician. This 3 and 4/12-year-old girl presented with fatigue, abdominal pain, vomiting, constipation, headaches, polydipsia, nocturia, and irritability. During the previous 5 weeks, she had received a total 3 600 000 IU for apparent failure to thrive. Severe hypercalcemia (17.4 mg/dL) was treated with intravenous saline, furosemide, and pamidronate. Two weeks after discharge, serum calcium concentration had normalized (9.6 mg/dL). Similar cases of hypervitaminosis D in children after high-dose supplementation for inappropriate indications are reported elsewhere.[6] In 1 recent series, seven children aged 7.5 to 25 months were treated with 900 000 to 4 000 000 IU of vitamin D for failure to thrive and developmental delay. All 7 had hypercalcemia and hypercalciuria; nephrocalcinosis was present in 5 patients.[7]

Upward modification of target thresholds for serum 25-hydroxyvitamin D levels in recent years has led to an increase in the diagnosis of apparent vitamin D deficiency, and an increased use of vitamin D supplements. Benefits of this approach have yet to be demonstrated by randomized controlled trials.[8] Recently, the *Dietary Reference Intakes for Calcium and Vitamin D* (Institute of Medicine, 2011)[9] has provided evidence-based guidance for requirements, upper tolerable limits of daily exposure, and target circulating 25-OHD levels for both adults and children. The adequate intake of vitamin D for infants <1 year of age is 400 IU/day; the RDA is 600 IU for children aged 1 to 18 years, as well as through most of adulthood; the target serum 25-OHD level is recommended as 20 ng/mL (50 nmol/L).[3]

Because of the risk of toxicity, a conservative approach to therapy for vitamin D deficiency in infants and young children should be considered. Lower range of dosing, adjusted by appropriate biochemical monitoring is suggested, and should include the measurement of serum calcium within the first few weeks of therapy. Measurement of serum phosphorus and alkaline phosphatase activity are helpful in the assessment of expected biochemical and skeletal response to therapy. Most notably, hypercalcemia occurred in each of our cases with the use of dosages within well-recognized recommendations for treating vitamin D-deficient rickets, suggesting that treatment guidelines for vitamin D deficiency may require modification for this age group.

CONCLUSIONS

The incidence of hypervitaminosis D described in this series is far greater than we would expect on the basis on our own clinical observations during the previous 20 years. Vitamin D therapy, even when provided within established treatment guidelines, has the potential to lead to toxicity in small children when not monitored. We raise the consideration that with heightened awareness of vitamin D deficiency, and increased prescribing of pharmacologic vitamin D to small children, an increased risk of toxicity may also be emerging. Recommendations for vitamin D therapy require reexamination for safety in this age group.

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