

Acute Vitamin D Intoxication in a Child

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ABSTRACT. We present the unique case of a previously healthy, 2-year-old boy with resistant hypercalcemia and hypertension resulting from an unintentional overdose with an imported vitamin D supplement. The patient presented initially to the emergency department with colic and constipation and was discharged after a benign physical examination. The symptoms persisted and, on the second visit, the patient was found to have a serum calcium level of 14.4 mg/dL. Despite therapy with intravenously administered 5% dextrose solution at one-half normal strength, furosemide, calcitonin, and hydrocortisone, the calcium concentration increased to 15.0 mg/dL on the second hospital day and did not decrease until the fourth hospital day, when it fell to 13.9 mg/dL. The vitamin D concentration peaked at 470 ng/mL on hospital day 3. With additional questioning, the mother revealed that she had been giving her son a daily dose of 1 ampule of Raquiferol, an imported vitamin D supplement, instead of the recommended 2 drops per day. Each ampule contained 600 000 IU of vitamin D; therefore, the boy received a total of 2 400 000 IU over 4 days. The patient's hypercalcemia persisted for 14 days and was complicated by persistent hypertension. No renal, cardiac, or neurologic complications were noted. At discharge, the vitamin D concentration was still elevated at 389 ng/mL and the total calcium level had decreased to 11 mg/dL. The boy made a complete clinical recovery. This case highlights the need for caution when using imported and/or unregulated medicines, as well as the dangers of parental dosing errors. *Pediatrics* 2005; 116:e453–e456. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2580; *vitamin D, overdose*.

ABBREVIATION. AAP, American Academy of Pediatrics.

With the resurgence of breastfeeding in the United States,¹ vitamin D supplementation is once again an important issue, especially considering the parallel increase in the number of reported cases of nutritional rickets.^{2–6} The American

Academy of Pediatrics (AAP) recently issued a new policy on vitamin D supplementation that recommends that all breastfeeding infants and nonbreastfeeding infants who drink <500 mL (<16½ oz) of vitamin D-fortified formula or milk per day should receive 200 IU of vitamin D per day.⁷ Although the skin has the ability to metabolize cholesterol to a vitamin D precursor, it is unclear exactly how much sunlight one needs daily to metabolize sufficient amounts of vitamin D effectively.⁸ In addition, health care providers and organizations, including the Centers for Disease Control and Prevention, have recommended decreased exposure to direct sunlight and the liberal use of sunscreens to prevent skin cancer.⁹ Because vitamin D is used so readily, it is important to understand how dosing errors can lead to overdoses with potentially life-threatening consequences.

Vitamin D is 1 of 4 fat-soluble vitamins. With parathyroid hormone, it regulates calcium homeostasis tightly. When the serum calcium level is low, calcitriol, the biologically active form of vitamin D, restores homeostasis through increased dietary calcium absorption through the gut and through increased bone resorption. Dietary sources of vitamin D are limited to fish, oysters, and dairy products. In the United States, milk is fortified with vitamin D, and some forms of butter, margarine, cereals, and fruit juices also are fortified. Unfortunately, most individuals in the United States do not eat the necessary 2 servings of a vitamin D-fortified food in a day to ensure adequate dietary intake of vitamin D.¹⁰ To make up for this deficit, these people should rely on adequate sun exposure; however, if these patients adhere to the recommendation of the Centers for Disease Control and Prevention on decreasing direct sun exposure, then they would need a dietary supplement of vitamin D to ensure proper bone health.

Unintentional vitamin D poisoning has been associated with overfortification of milk,^{11,12} adulteration of table sugar,¹³ and contamination of cooking oil^{14–16} and with use of an over-the-counter supplement by an adult.¹⁷ We present the unique case of an unintentional vitamin D overdose in a child, caused by improper dosing with an imported vitamin D supplement.

CASE REPORT

A previously healthy, 2-year-old, Hispanic boy was brought to the emergency department by his mother because of constipation and abdominal pain. During the previous 3 days, he had experienced vomiting, constipation, lethargy, and abdominal pain. With the exception of slightly elevated blood pressure, his physical

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examination results were benign. The patient was discharged with a diagnosis of constipation, and his mother was instructed to follow up with his pediatrician regarding his blood pressure. The boy was brought back to the emergency department the next day because of continued and worsening abdominal pain. The review of systems was significant for a loss of appetite but otherwise yielded negative results. The mother denied that the child had fever, diarrhea, or seizure-like activity. She indicated that the only medication her son had been taking was a vitamin D supplement, Raquiferol (Spedrog Caillon Laboratories), which is sold normally in Latin American countries and which she had obtained from a local bodega. She started giving him this medicine to promote good health and strong bones. The mother administered 1 ampule of Raquiferol per day for ~4 days, with the last dose being administered 8 days before admission. Each ampule contained 600 000 IU of vitamin D; therefore, the boy received a total of 2 400 000 IU over 4 days.

The physical examination revealed an age-appropriate young boy who was crying intermittently but could be consoled. He weighed 14.5 kg (90th percentile). Vital signs were as follows: blood pressure, 139/98 mm Hg; pulse, 88 beats per minute; respiratory rate, 16 breaths per minute; temperature, 97.6°F. Other significant findings in the physical examination included a nontender nondistended abdomen with normal active bowel sounds and nonfocal neurologic examination results.

Laboratory testing showed a serum Ca^{2+} concentration of 14.4 mg/dL (normal: 8.4–10.2 mg/dL). Complete blood count and electrolyte concentrations were within normal limits, as follows: Na^+ , 139 mEq/L; K^+ , 3.7 mEq/L; Cl^- , 102 mEq/L; CO_2 , 28 mEq/L; blood urea nitrogen, 13 mg/dL; creatinine, 0.5 mg/dL; glucose, 107 mg/dL; Mg^{2+} , 1.3 mg/dL. An electrocardiogram showed normal sinus rhythm, with a regular rate and normal intervals.

With additional investigation, it was noted that the Raquiferol package instructions indicated that the recommended dosage was 2 drops from an ampule per day. On the basis of this history and the physical examination and laboratory investigation results, hypercalcemia caused by unintentional vitamin D overdose was diagnosed, and the patient was admitted to the PICU for treatment.

Additional testing at admission showed a vitamin D concentration of 106 ng/mL (normal: 10–68 ng/mL). The immunochemiluminometric assay that was used (LabCorp, Research Triangle Park, NC) measures 25-hydroxyvitamin D and its 24,25-, 25,26-, and 1,25-dihydroxy metabolites. The physiologic concentrations of these metabolites are insignificant and therefore do not affect the accuracy of the 25-hydroxyvitamin D measurements.

During his 2-week hospitalization, the patient was treated with intravenously administered fluids (5% dextrose solution at one-half normal strength at 1.5 times maintenance), furosemide, calcitonin, and intravenously administered hydrocortisone. Despite these therapies, the total calcium level increased to 15.0 mg/dL on hospital day 2 and did not decrease until the 4th hospital day, at which time it decreased to 13.9 mg/dL. The vitamin D concentration did not peak at 470 ng/mL until hospital day 3 (Fig 1) because the half-life of vitamin D is ~30 to 60 days.⁸ During his stay, the patient remained asymptomatic except for occasional colic and persistent hypertension. When he was discharged, his vitamin D level was still elevated at 389 ng/mL and his total calcium concentration was 11 mg/dL. His discharge instructions included avoidance of products containing vitamin D and use of sunscreen for 3 to 4 months. At the 3-month follow-up visit, his total serum calcium concentration was 12 mg/dL.

DISCUSSION

Guidelines issued by the AAP and the National Academy of Sciences indicate that all breastfeeding infants and nonbreastfeeding infants who drink <500 mL (<16 $\frac{1}{3}$ oz) of vitamin D-fortified formula or milk per day should receive 200 IU of vitamin D per day.⁷ Vitamin D has a median lethal dose of 21 mg/kg¹⁸ and, in overdose, affects all major organ systems. The symptoms of vitamin D toxicity stem from the deposition of calcium phosphate crystals in soft tissues throughout the body,¹⁰ which can occur once the calcium-phosphate product is >60 mg/dL.¹⁹ Early symptoms of hypercalcemia include anorexia, nausea, vomiting, weakness, lethargy, constipation, and nonspecific aches and pains. Renal function can become impaired as a result of nephrocalcinosis. Vascular calcification leads to renal hypertension. Because vitamin D is lipophilic and is stored in fat tissues, the effects of vitamin D toxicity can persist \geq 2 months after the exogenous source is removed.

The patient described in this report was mistakenly given 600 000 IU of an imported vitamin D product each day for 4 days. Each drop contains

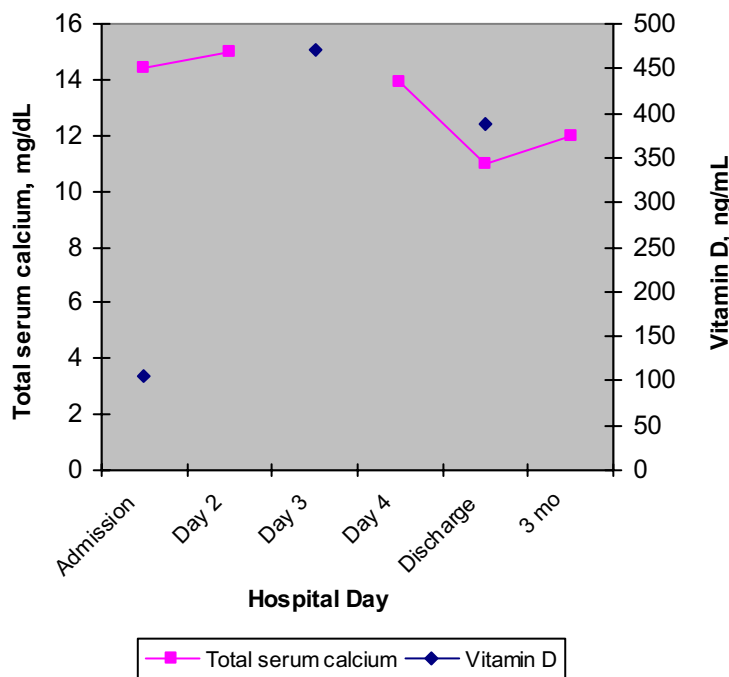


Fig 1. Trends of total serum calcium and vitamin D concentrations in a pediatric overdose.

~2500 IU of vitamin D, and each ampule contains 9 mL (15 mg) or 600 000 IU. The package instructions indicate that adults should be given 1 or 2 drops once per day (2500–5000 IU). The adequate intake of vitamin D for toddlers is 200 IU/day.²⁰ Therefore, our patient received 3000 times the daily adequate intake of vitamin D. He received 300 times the daily tolerable level of intake for vitamin D, as defined by the Institute of Medicine (the upper level of tolerable intake for toddlers, as well as for adolescents and adults, is 2000 IU per day; for infants, this level is to 1000 IU per day).²⁰ The vitamin D analog ergocalciferol, as purchased by the mother, was at the concentration needed for treatment of nutritional rickets, not for routine dietary supplementation. Normally this product requires a prescription in the United States; however, an Internet search for the supplement clearly shows that it is readily available from many other sources.

Treatment for vitamin D toxicity includes immediate removal of the exogenous source, intravenous fluid hydration, loop diuretics (thiazides can promote calcium retention), glucocorticoids, and a low-calcium diet. Glucocorticoids decrease the production of 1,25-dihydroxyvitamin D₃, which decreases dietary absorption of calcium. It also prevents calcium from being resorbed in the renal tubules, thereby promoting the urinary excretion of calcium.

Exogenous calcitonin can also be used. The associated risks, specifically the risk of allergic reactions, have decreased because it no longer is derived from salmon but now is available as recombinant human calcitonin.²¹ It inhibits bone resorption and blocks release of calcium and phosphate into the serum. The use of bisphosphonates, such as pamidronate, is accepted widely for adults, but uses in children have been only anecdotal^{22,23} and thus the safety is unknown. Hemodialysis can be used to treat hypercalcemia and can lower serum calcium levels rapidly. Because rebound hypercalcemia is predictable after vitamin D intoxication, hemodialysis should be reserved for life-threatening, medically unmanageable indications, such as acute or chronic renal failure and hypercalcemic crisis.^{24,25} Hemodialysis, exchange transfusions, and bisphosphonates were not used in this case because the patient responded to therapy eventually.

As awareness of the AAP guidelines increases in the general population, more people may start to use vitamin D supplements without physician supervision. As this case report demonstrates, acute intoxication can occur as a result of parental dosing errors. Vitamin D is a beneficial supplement and is safe when used correctly at its recommended doses (200–1000 IU for infants and 2000 IU for all others). Vitamin D toxicity occurs over days of ingesting thousands of international units of vitamin D; therefore, it is unlikely that patients will overdose with the doses of vitamin D found in daily multivitamins or foods fortified with vitamin D. However, if a patient presents with symptoms consistent with vitamin D toxicity, then strong clinical suspicion with a history that reveals the use of a vitamin D supplement

should make clinicians consider this condition in the differential diagnosis. Vitamin D supplements used for the treatment of rickets are too concentrated for use as a routine supplement. Although it is not necessary to educate all parents about the symptoms of acute vitamin D intoxication, in appropriate situations they should be informed about the possible dangers of vitamin D and the importance of careful dosing.

Because of cultural and language barriers, lack of health insurance, inadequate access to health care, or insufficient funds to purchase prescription medicines from traditional pharmacies, many people are looking for nontraditional sources of medications. Therefore, physicians must be diligent in knowing what medicines, supplements, and herbal remedies their patients are taking and should not hesitate to examine the containers to verify the ingredients and recommended dosages. Physicians should also warn patients to avoid unregulated or unfamiliar supplements and medicines and should advise them to read carefully the boxes and labels of the products they choose to use. Individuals who have questions about medicines or supplements should talk with their health care providers before taking them or giving them to someone in their care.

REFERENCES

1. Wright AL. The evidence for breastfeeding: the rise of breastfeeding in the United States. *Pediatr Clin North Am.* 2001;48:1–12
2. Welch TR, Bergstrom WH, Tsang RC. Vitamin D-deficient rickets: the reemergence of a once conquered disease. *J Pediatr.* 2000;93:143–145
3. Rowe PM. Why is rickets resurgent in the USA? *Lancet.* 2001;357:1100
4. Carvalho NF, Kennedy RD, Carrington PH, Hall DE. Severe nutritional deficiencies in toddlers resulting from health food milk alternatives. *Pediatrics.* 2001;107(4). Available at: www.pediatrics.org/cgi/content/full/107/4/e46
5. Tomashek KM, Nesby S, Scanlon KS, et al. Nutritional rickets in Georgia. *Pediatrics.* 2001;107(4). Available at: www.pediatrics.org/cgi/content/full/107/4/e45
6. Shah M, Salhab N, Patterson D, Seikaly MG. Nutritional rickets still afflict children in north Texas. *Tex Med.* 2000;96:64–68
7. Gartner LM, Greer FR, American Academy of Pediatrics, Section on Breastfeeding and Committee on Nutrition. Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake. *Pediatrics.* 2003;111:908–910
8. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr.* 1999;69:842–856
9. Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention. Guidelines for school programs to prevent skin cancer. Available at: www.cdc.gov/cancer/nscep/guidelines.htm. Accessed March 2, 2005
10. Office of Dietary Supplements, National Institutes of Health. Dietary supplement fact sheet: vitamin D. Available at: <http://ods.od.nih.gov/factsheets/vitaminD.asp>. Accessed March 1, 2005
11. Blank S, Scanlon KS, Sinks TH, et al. An outbreak of hypervitaminosis D associated with the overfortification of milk from a home delivery dairy. *Am J Public Health.* 1995;85:656–659
12. Jacobus CH, Holick MF, Shao Q, et al. Hypervitaminosis associated with drinking milk. *N Engl J Med.* 1992;326:1173–1177
13. Vieth R, Pinto TR, Reen BS, et al. Vitamin D poisoning by table sugar. *Lancet.* 2002;359:672
14. Down PF, Polak A, Regan RJ. A family with massive acute vitamin D intoxication. *Postgrad Med J.* 1979;55:897–902
15. Pettifor JM, Bickle DD, Ross FP, et al. Serum levels of free 1,25-dihydroxyvitamin D in vitamin D toxicity. *Ann Intern Med.* 1995;122:511–513
16. Thomson RB, Johnson JK. Another family with acute vitamin D intoxication: another cause of familial hypercalcemia. *Postgrad Med J.* 1986;62:1025–1028

17. Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. *N Engl J Med*. 2001;345:67–68
18. Dorman DC. Toxicology of selected pesticides, drugs, and chemicals: anticoagulant, cholecalciferol, and bromethalin-based rodenticides. *Vet Clin North Am Small Anim Pract*. 1990;20:339–352
19. Brancaccio D, Tetta C, Gallieni M, Panichi V. Inflammation, CRP, calcium overload and a high calcium-phosphate product: a “liaison dangereuse.” *Nephrol Dial Transplant*. 2002;17:201–203
20. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington, DC: National Academy Press; 1999
21. Wuster C, Schurr W, Scharla S, et al. Superior local tolerability of human versus salmon calcitonin preparations in young healthy volunteers. *Eur J Clin Pharmacol*. 1991;41:211–215
22. Lee DC, Lee GY. The use of pamidronate for hypercalcemia secondary to acute vitamin D intoxication. *Clin Toxicol*. 1998;36:719–721
23. Mathur M, Sykes JA, Saxena VR, et al. Treatment of acute lymphoblastic leukemic-induced extreme hypercalcemia with pamidronate and calcitonin. *Pediatr Crit Care Med*. 2003;4:252–255
24. Behrman RE, Kliegman RM, Jenson HB. Calcium. In: Behrman RE, Kliegman RM, Jenson HB, ed. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia, PA: WB Saunders; 2004:208–216
25. Ziegler R. Hypercalcemic crisis. *J Am Soc Nephrol*. 2001;12(suppl 17): S3–S9

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