The Lack of Vitamin D Toxicity with Megadose of Daily Ergocalciferol (D_2) Therapy: A Case Report and Literature Review

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Abstract: The maximum daily dose of vitamin D currently recommended is 2000 IU. Ergocalciferol (D2) 50,000 IU orally weekly for 8–12 weeks is often used to treat vitamin D deficient patients (25(OH) vitamin D <20 ng/mL). The lack of vitamin D toxicity after massive doses of ergocalciferol has yet to be reported in the literature. We report a case of a 56-year-old woman who received supratherapeutic doses of ergocalciferol (150,000 IU orally daily) for 28 years without toxicity. We discuss the possible mechanisms which may account for a lack of toxicity despite intake of massive daily doses of ergocalciferol in this patient.

Key Words: cholecalciferol, ergocalciferol, hypervitaminosis D, vitamin D, vitamin D toxicity

The presence of widespread vitamin D deficiency as a global problem is well documented. Given the lack of sunlight exposure and inadequate amounts ingested, many individuals have chronically low levels of vitamin D. It is widely believed that the current recommendations for vitamin D intake, while appropriate for preventing rickets and osteomalacia, are inadequate for optimal health. Adequate vitamin D replacement has the potential to ameliorate many chronic diseases, including autoimmune illness, and several types of cancer. Vitamin D replacement is also used to maintain adequate calcium homeostasis. Hypocalcemia seen after thyroidectomy or parathyroidectomy may be accompanied by hypovitaminosis D. We report a patient with a massive daily intake of ergocalciferol for hypoparathyroidism post-thyroidectomy.

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Accepted January 14, 2009.

0038-4348/0−2000/10200-0765

Case Report

A 56-year-old Caucasian female was referred to the endocrinology clinic due to concerns by allied healthcare providers that the dose of vitamin D she was receiving appeared to be supratherapeutic and possibly toxic. The patient had no complaints. The patient indicated that she was compliant with all her medications and that her vitamin D dose had been refilled within the last year without a change in dose. She had a previous medical history of thyroid cancer status post thyroid resection in 1980, hypoparathyroidism, hypothyroidism, gastroesophageal reflux disease, arthritis, and postmenopausal estrogen deficiency. They attempted to reimplant one of the parathyroid glands in her neck but this was believed to be unsuccessful. Soon after her surgery she developed tetany secondary to hypocalcemia, requiring her to receive calcium supplements and vitamin D for life. She had been taking levothyroxine 0.05 mg and vitamin D 150,000 IU orally daily for 28 years. She did not receive any nutritional counseling but was told to take two Tums tablets each containing 1.25 gm (500 mg elemental calcium) of calcium carbonate which would be equivalent to 1000 mg of elemental calcium three times daily. She took the Tums tablets as prescribed for 4 years, then discontinued them due to a desire to obtain her calcium

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Key Points

- Long-term vitamin D (ergocalciferol) taken at supratherapeutic doses failed to result in intoxication or hypercalcemia.
- This suggests that ergocalciferol may be less potent than cholecalciferol.
- Substituting cholecalciferol for ergocalciferol at the same dosages may result in toxic levels of vitamin D, especially if given with calcium.

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through her meals instead. She consistently consumed 2–3 cups of low-fat milk per day (300 mg calcium per cup). She consumed cheese (200 mg/oz), yogurt (450 mg/oz), ice cream (100 mg/0.5 cup), and spinach (240 mg/cup) when available in order to keep her calcium level elevated. Her estimated daily intake of calcium through her diet was 1 gm/day. Given the vulnerability to hypercalcemia with calcium supplements we verified that she was not taking any calcium-containing antacids. Drinka et al[1] reported the occurrence of hypercalcemia in nursing home residents when calcium supplements were used with 50,000 IU of ergocalciferol daily.

The vitamin D preparation she had received over the years was vitamin D2 (ergocalciferol). She had received various brands and manufacturers over the years. The current brand she was taking was ergocalciferol 50,000 IU tablet made by Barr Laboratories. The dose she received was equivalent to 3.75 mg (150,000 IU) of vitamin D2 each day. The patient provided her current ergocalciferol bottle and the tablets remaining in the bottle plus her regular refills at appropriate times were consistent with daily use in the amount indicated by the patient. She was postmenopausal and had been taking Prempro 0.45/1.5 mg by mouth every day. She had been taking omeprazole 20 mg daily and naproxen 500 mg by mouth twice daily. The use of naproxen can increase the risk of developing renal insufficiency; however, her renal function was normal.

On presentation, she did not complain of any signs or symptoms of hypercalcemia (fatigue, depression, anorexia, nausea, constipation, polyuria, polydipsia, or muscle weakness) or hypocalcemia (paresthesias of the lips or extremities, muscle spasm, carpopedal spasm, seizures, weakness, or abdominal cramping). She did state that she had felt more "hyper," and had trouble sleeping at night. She denied palpitations, diaphoresis, tremor, heat intolerance, unintentional weight loss, irritability, impaired concentration, or diarrhea. Her physical exam was unremarkable with stable vital signs. Serial serum calcium, ionized calcium and 25(OH)D levels were done and the results are listed in the Table.

The 25(OH)D assay utilized by LabCorp was an immunochemiluminometric assay. This assay measures vitamin D2 and D3 with equal sensitivity. The following additional laboratory values were observed: albumin 4.2 g/dL (3.5–5), phosphorus 3.9 mg/dL (2.7–4.5), magnesium 2.0 mg/dL (1.7–2.2), thyroid stimulating hormone 0.54 mcIU/mL (0.35–5.5), free T4 1.3 ng/dL (0.89–1.76), serum creatinine 0.9 mg/dL (0.6–1), 25(OH), 24-hour urinary calcium 160 mg, (100–300) 24-hour urine creatinine 1.3 gm (0.8–1.8), urinary volume of 1800 cc (600–1600), alkaline phosphatase 74 IU/L, (38–126) hemoglobin 14.2 mg/dL (11.8–15.8) and hematocrit 42%. (35–45) Since the patient was not hypercalcemic, no assessment of 1,25 dihydroxyvitamin D were done. Her intact PTH was normal at 28 pg/mL. (11–54) This may indicate some residual PTH secretion, possibly by the parathyroid gland reimplanted in her neck years earlier. Since the patient was not hypercalcemic and renal function was normal we did not obtain a renal ultrasound or x-ray. Her last bone mineral density measurement performed twice in the last year was within normal limits. We discontinued her ergocalciferol 150,000 IU and changed her medical regimen to include calcium carbonate 2.5 gm three times daily with food and vitamin D3 (cholecalciferol) 4000 IU/daily. A repeat serum calcium level 2 weeks after this change was 9.2 mg/dL.

Discussion

Vitamin D is available for oral ingestion in two chemical types, cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Cholecalciferol is produced naturally in human skin exposed to ultraviolet B light. It is added to various dietary supplements (such as multivitamins) and fortified foods (such as milk). Ergocalciferol is derived from the yeast and plant sterol precursor, ergosterol. Ergocalciferol is commonly used in North America as a weekly supplement (50,000 IU) for rapid induction of a vitamin replete state in patients with vitamin D deficiency. Serum 25(OH)D concentration is normally maintained within a narrow range of 30–100 ng/mL across vitamin D doses of 800 IU to the physiologic limit of 20,000 IU/day.[2] The Institute of Medicine and the Food and Nutrition Board has indicated a safe tolerable upper intake level of 2000 IU/day for vitamin D.[3] It is clear that daily production of vitamin D through UV skin exposure can reach 10,000 IU daily. Vieth[4] has suggested that the upper limit should therefore be 10,000 IU daily and that this dose does not pose a threat to health.

In addition to the increasingly better documented health benefits of a vitamin D replete state, vitamin D supplementation may be indicated for hypoparathyroidism following thyroidectomy or parathyroidectomy due to either intentional

Table. Patient's lab values

	Week 1	Week 2	Week 3
Calcium (normal 8.4–10.2 mg/dL)	9.7	9.2	9.8
Ionized calcium (normal 4.5–5.6 mg/dL)	4.8	4.8	5.1
25(OH)D (normal 30–100 ng/mL)	107	107	—

removal or unintentional damage to the parathyroid glands. In many cases of hypoparathyroidism, the onset of hypercalciuria may limit the dose of vitamin D used. Clinicians have traditionally aimed to keep the serum calcium levels in the lower part of the normal range to minimize this problem. While our patient had normal levels of PTH, the lack of clinical or biochemical toxicity despite receiving high doses of vitamin is perplexing and may relate to the minimally elevated 25(OH) vitamin D level. To our knowledge, this is the first reported case of lack of significant toxicity despite the use of massive doses of daily ergocalciferol (vitamin D2) over a prolonged period of time. Vieth[2] reviewed many vitamin D studies and found that there were no adverse effects from 25(OH) vitamin D concentrations <56 ng/mL. The published cases of vitamin D toxicity with hypercalcemia all involve vitamin D intake of >1 mg (40,000 IU)/day and 25(OH)D concentrations >88 ng/mL. Veith lists many case reports of patients receiving chronic high-dose vitamin D doses equal to or greater than the patient in this case; however, they all had toxic levels of 25(OH)D. It is possible that cholecalciferol may have been used rather than ergocalciferol in some of these cases.

Both calciferols appear to be absorbed with equal efficacy, but ergocalciferol may be less potent.[4] Romagnoli et al[5] studied variations in serum calciotropic hormones after a single, very large dose of ergocalciferol or cholecalciferol in the elderly. Cholecalciferol was almost twice as potent as ergocalciferol in increasing serum 25(OH)D when administered either by mouth or intramuscularly. Furthermore, in many adults with cystic fibrosis, 400,000 to 800,000 IU of oral ergocalciferol over 2 months failed to correct vitamin D deficiency in patients with cystic fibrosis,[6] although decreased intestinal absorption may have played a role in these results. Houghton et al[7] proposed against use of ergocalciferol as a supplement. In contrast, Holick et al[8] reported that the ability of ergocalciferol to raise the 25(OH)D level was similar to cholecalciferol, albeit at lower cholecalciferol doses of around 1000 IU daily. Armas et al[9] reported that a single dose of 50,000 IU of ergocalciferol and cholecalciferol were equally effective in raising 25(OH)D in the first three days after administration. However, with repeated analysis, the 25(OH)D level continued to rise over the next 30 days in the cholecalciferol group while the levels seen in the ergocalciferol group decreased significantly.

This relative lack of toxicity of ergocalciferol has also been documented in other species. In reports of vitamin D intoxication in horses, the data suggests that ergocalciferol is likely to be less toxic than cholecalciferol.[10] Similarly, in Rhesus monkeys, cholecalciferol was significantly more toxic than ergocalciferol when used in very large daily doses.[11] It is therefore possible that ergocalciferol was metabolized to a greater degree and this minimized toxicity. In studies done by Morris,[12] cats discriminate against ergocalciferol and use it with an efficiency of 0.7 of that of cholecalciferol to maintain plasma 25(OH)D concentration. This may be due to the differences in affinity of the binding protein for the metabolites of the two forms of vitamin D.

We believe the patient in this report was compliant with her medication as determined by repeated interviews and reflected by her normal TSH level from the continued intake of levothyroxine in the absence of a thyroid gland. She did not give us any indication that she was not consistent in her medication compliance since she was afraid of developing the tetany she had experienced years earlier. There was no clinical indication of malabsorption as a consequence of steatorrhea or celiac disease. Cholestatic liver disease, extrahepatic biliary obstruction and enteritis were not present to impair absorption and disrupt enterohepatic circulation. Since vitamin D is hydroxylated in the liver, a patient with severe parenchymal or obstructive disease may have impaired metabolism of vitamin D. No indication of liver impairment was seen in this patient. End organ insensitivity (resistance) to vitamin D is rare and would likely have been demonstrated as rickets at an early age.

We believe the lack of vitamin D toxicity was the likely result of reduced inherent efficacy of ergocalciferol compared to cholecalciferol combined with the lack of significant calcium supplementation. Houghton et al[7] discuss the findings in animal models that vitamin D2 metabolites have a weaker binding affinity for plasma vitamin D2 binding protein resulting in shorter circulating half-lives and an increased rate of clearance from the circulation. They also state that vitamin D3 has the ability to maintain higher 25(OH)D concentrations over time since hepatic 25-hydroxylase, the first enzymatic step in the conversion of vitamin D to the biologically active form 1,25 dihydroxyvitamin D, has a five times higher affinity for vitamin D3 than vitamin D2. Earlier studies did indicate the occurrence of toxicity with ergocalciferol, although it was possible that the differences from the more recent studies may relate to methodological differences such as vitamin D assays.[13]

If there is a change from using ergocalciferol (D2) to cholecalciferol (D3) at high doses for pharmacologic replacement in North America, we advocate that great care is taken given the likely enhanced potency of cholecalciferol compared to ergocalciferol to induce hypercalcemia, especially if calcium supplements are used. The maximally tolerated dose of vitamin D is controversial in light of the current literature and there is no convincing evidence for the safety of the dose of ergocalciferol used in this reported case.

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"When you're in love you never really know whether your elation comes from the qualities of the one you love, or if it attributes them to her; whether the light which surrounds her like a halo comes from you, from her, or from the meeting of your sparks."

—Natalie Clifford Barney