Severe Hypercalcemia Following Vitamin D Supplementation in a Patient With Multiple Sclerosis

A Note of Caution

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Objective: To describe a patient with multiple sclerosis (MS) who developed severe hypercalcemia, attributed to the additive effect of 5500 IU of cholecalciferol and 2020 mg of calcium daily.

Design: Case report.

Setting: University hospital.

Patient: A 58-year-old woman with MS and osteoporosis presenting with acute-onset tremors and confusion.

Main Outcome Measures: Serum calcium and 25-hydroxyvitamin D levels.

Results: The patient’s corrected serum calcium level was 15.2 mg/dL (reference range, 8.7-10.1 mg/dL; to convert to millimoles per liter, multiply by 0.25), and her 25-hydroxyvitamin D level was 103 ng/mL (to convert to nanomoles per liter, multiply by 2.496). The results of extensive laboratory tests to rule out hyperparathyroidism, malignant neoplasms, and other causes of hypercalcemia were unrevealing.

Conclusions: It is common practice to prescribe high-dose cholecalciferol to MS patients for its possible role in immunomodulation and relapse-rate reduction. Nevertheless, cholecalciferol may increase serum calcium, and there seems to be an additive effect when patients simultaneously use calcium supplements. This case underscores the need for physicians to be attentive to the possibility of hypercalcemia in patients treated with both high-dose cholecalciferol and calcium.

Arch Neurol. 2012;69(1):129-132

IN LIGHT OF RECENT EPIDEMIOLOGIC EVIDENCE DEMONSTRATING THAT LOW 25-HYDROXYVITAMIN D (25-OH D) SERUM LEVELS ARE ASSOCIATED WITH MULTIPLE SCLEROSIS (MS) SUSCEPTIBILITY1-3 AND INCREASED CLINICAL DISEASE ACTIVITY,4,5 IT HAS BECOME MAINSTREAM PRACTICE FOR NEUROLOGISTS TO AGGRESSIVELY PRESCRIBE CHOLECALCIFEROL SUPPLEMENTS IN PATIENTS WITH MS. PATIENTS WITH MS ARE ALSO PARTICULARLY SUSCEPTIBLE TO LOW BONE MINERAL DENSITIES, LIKELY DUE TO COMPLICATIONS OF IMMOBILITY.6 AS A RESULT, MANY MS PATIENTS TAKE CALCIUM SUPPLEMENTS FOR BONE HEALTH, WHICH MAY INCLUDE ADDITIONAL CHOLECALCIFEROL. ALTHOUGH DOSING VARIES BY PRACTICE, MS SPECIALISTS OFTEN PRESCRIBE SUPPLEMENTAL CHOLECALCIFEROL TO PATIENTS WITH 25-OH D SERUM LEVELS LESS THAN 30 NG/mL (TO CONVERT TO NANOMOLES PER LITER, MULTIPLY BY 2.496). AT MANY INSTITUTIONS (INCLUDING OURS), THE GOAL OF SUPPLEMENTATION IS TO ACHIEVE SERUM LEVELS OF APPROXIMATELY 40 TO 60 NG/mL, BASED ON OBSERVATIONAL DATA THAT 25-OH D LEVELS HIGHER THAN 40 NG/mL ARE PROTECTIVE IN MS AND THAT LEVELS UP TO 60 NG/mL ARE ASSOCIATED WITH LOWER RELAPSE RISK.2,4,5 WE REPORT A CASE OF AN MS PATIENT WHO PRESENTED WITH SEVERE SYMPTOMATIC HYPERCALCEMIA DUE TO THE INTERACTION OF HIGH-DOSE CHOLECALCIFEROL AND CALCIUM SUPPLEMENTS.

REPORT OF A CASE

A 58-year-old, right-handed woman with progressive MS, hypertension, and osteoporosis presented to the emergency department with face and arm tremors and expressive language difficulty for 2 hours. She also had experienced a gradual decline during the previous 2 weeks, characterized by difficulty with transfers, impaired balance, abdominal discomfort, decreased appetite, and lethargy. The patient was diagnosed as having MS in 2001 and experienced progressive asymmetric limb weakness, leaving her wheelchair dependent but able to perform transfers. Other symptoms included numbness,
Vitamin D is predominantly synthesized from 7-dehydrocholesterol via exposure of the skin to UV-B solar radiation. Figure 2 demonstrates vitamin D metabolism and its subsequent effect on calcium use. Twenty minutes of whole-body UV-B exposure for a light-skinned person during the summer produces at least 10 000 IU of vitamin D, whereas a food serving usually only provides 40 to 400 IU of vitamin D.7 Oral supplementation requirements vary depending on age, body weight, body fat, skin color, season, latitude, and sun exposure.

Overexposure to vitamin D produces symptomatic hypercalcemia, with possible weakness, fatigue, depression, confusion, stupor or coma, polyuria, nephrolithiasis, renal failure, ectopic calcification, conjunctivitis, fever, chills, anorexia, nausea, vomiting, and constipation. Although our patient had several typical symptoms of hypercalcemia, acute onset of tremor and language difficulty were unusual manifestations. We could not com-
completely exclude a transient ischemic attack or a seizure, but the patient’s laboratory evaluation and prompt recovery after rehydration make hypercalcemia the most likely cause of her symptoms.

Most patients with symptomatic hypercalcemia have an underlying malignant neoplasm or hyperparathyroidism, but these diagnoses were unlikely given our patient’s low serum PTH and normal PTH-related protein levels. Her laboratory findings were not suggestive of hyperparathyroidism, adrenal insufficiency, end-stage renal disease, or multiple myeloma. Paget disease, granulomatous diseases, familial hypocalciuric hypercalcemia, end-stage renal disease, milk-alkali syndrome, thiazide diuretics, and lithium also did not fit with this case. Although systematic safety data do not exist for compounded immediate-release 4-aminopyridine, the sustained-release dalfampridine (Ampyra) has not been associated with any laboratory abnormalities, including hypercalcemia. This extensive evaluation, together with the maintenance of normal calcium levels for more than 2 months after discontinuing use of high-dose cholecalciferol and calcium supplementation (but with continuation of her 4-aminopyridine therapy), suggest that our patient's marked hypercalcemia was caused by the additive effects of her cholecalciferol and calcium supplementation.

The cutoffs for sufficiency and insufficiency of 25-OH D are not based on rigorous scientific studies or standardized among laboratories. Many experts believe that the toxic effects of vitamin D do not occur until levels exceed 150 ng/mL. Rare reports describe patients with symptomatic hypercalcemia from the toxic effects of vitamin D, and in the most extreme case hypercalcemia developed after use of 4000 IU of cholecalciferol daily for 2 months. However, many studies demonstrate tolerability and normal calcium levels in patients taking much higher doses of cholecalciferol, prompting recommendation for a no-adverse-effect level for cholecalciferol of 10 000 IU daily. Two studies specifically evaluated the safety of cholecalciferol in a combined group of 37 treated MS patients, and both found that up to 40 000 IU daily of cholecalciferol in addition to 1200 mg of elemental calcium could be tolerated during a 28-week period without a significant influence on serum or urinary calcium levels or serum creatinine levels. Study patients had no adverse outcomes despite serum 25-OH D levels that increased by an average of 130 ng/mL.

Our patient demonstrated hypercalcemia from the cumulative effect of 5500 IU of cholecalciferol and 2020 mg of elemental calcium daily. These are not unusually high doses of either supplement, and it is unclear why our patient experienced toxic effects from a dose of daily cholecalciferol that has been tolerated by many other patients. Possible reasons for our patient’s adverse response include her prolonged use of both high-dose cholecalciferol and calcium supplementation (for 2 years), her ingestion of almost twice the amount of elemental calcium taken by many patients, immobility, medication interactions, or her unique metabolism.

Well-powered, long-term randomized controlled trials are needed to define a dose of cholecalciferol that provides an optimal immunomodulatory benefit for MS without causing hypercalcemia, even when patients take supplemental calcium for skeletal health. The potential benefit of vitamin D analogues with low calcemic activity also warrants further study in an MS population. In the meantime, physicians should use caution when prescribing high-dose cholecalciferol in addition to elemental calcium in MS patients, and calcium and 25-OH D levels should be periodically monitored for early detection of oversupplementation. Prompt recognition and treatment of hypercalcemia are essential when treating patients with these medications.

Accepted for Publication: June 29, 2011.
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Financial Disclosure: None reported.

REFERENCES


