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.

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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,
Figure 1. The patient’s serum calcium (closed circles) and 25-hydroxyvitamin D (25-OH D) (open circles) levels over time.

postural instability, and bowel and bladder dysfunction. Cognitive and visual function were spared, and the patient had no history of seizures. Earlier treatments included interferon beta-1a (2001-2007) and off-label rituximab (2010). She had also been treated with 4-aminopyridine, 20 mg, twice daily for 2 years, which relieved fatigue and improved her motor skills. The patient was diagnosed as having osteoporosis in 2003, prompting use of elemental calcium, 600 mg, 3 times daily (sometimes combined with a 500 IU cholecalciferol supplement), zoledronic acid (Reclast) infusion (last dose in September 2010), and a supplement including cholecalciferol, 500 IU, and calcium, 220 mg (Centrum Silver). In March 2009, a 25-OH D level of 33.7 ng/mL was measured, and cholecalciferol, 5000 IU daily, was recommended.

On initial examination, the patient was alert, anxious, and frustrated by her language difficulties. Her blood pressure was 154/94 mm Hg, and other vital signs were normal. She was unable to name objects or repeat phrases, but she could point to pictures when given multiple choices. She could follow simple but not 3-step commands. Cranial nerve function was intact. A bilateral face mask was present on the right. Initial diagnostic findings. She exhibited hyperreflexia throughout, and a Babinski sign was present on the right. Initial diagnostic considerations included seizure, stroke, or MS exacerbation. Given the patient’s tremulousness, aphasia, and use of double the standard dose of 4-aminopyridine, the possibility of seizure was a particular concern.

An electrocardiogram revealed sinus tachycardia with a rate of 105/min. The results of portable chest radiography were unremarkable. Magnetic resonance imaging of the brain with and without gadolinium did not reveal acute hemorrhage, stroke, or progression of demyelinating disease since her last magnetic resonance image in February 2010. Her serum calcium level was markedly elevated at 14.6 mg/dL (15.2 mg/dL when corrected for an albumin level of 3.2 g/dL) (to convert to grams per liter, multiply by 10); reference range, 8.7-10.1 g/dL), and her ionized calcium level was 6.40 mg/dL (reference range, 4.64-5.20 mg/dL) (to convert both total and ionized calcium to millimoles per liter, multiply by 0.25). Her magnesium (1.3 mEq/L; reference range, 1.8-2.3 mEq/L; to convert to millimoles per liter, multiply by 0.5) and phosphorus (1.4 mg/dL; reference range, 2.4-4.6 mg/dL; to convert to millimoles per liter, multiply by 0.323) levels were low, whereas her serum urea nitrogen (48 mg/dL; reference range, 8-23 mg/dL; to convert to millimoles per liter, multiply by 0.357) and creatinine (1.32 mg/dL; reference range, 0.42-1.06 mg/dL; to convert to micromoles per liter, multiply by 88.4) levels were elevated. The patient’s serum parathyroid hormone (PTH) level was 4 pg/mL (reference range, 12-65 pg/mL; to convert to nanograms per liter, multiply by 1), and her 25-OH D level was 103 ng/mL (sufficiency >30 ng/mL, excess >150 ng/mL). Her thyrotropin, free thyroxine, cortisol, serum protein electrophoresis, urine protein electrophoresis, angiotensin-converting enzyme, and PTH-related protein levels were normal.

The patient was hydrated with 4 L of normal saline, together with magnesium and phosphorus repletion. After 2 to 3 hours, the tremors resolved and her language function recovered. Serum calcium levels and renal function promptly returned to normal after rehydration. The patient was amnestic for the entire period during which she had tremors and aphasia.

Before admission, the patient reported minimal sun exposure but ate fatty fish approximately 2 times per week. Age-appropriate cancer screening, including colonoscopy and mammography, was up to date. Six months before admission, her 25-OH D serum level was 83 ng/mL and her serum calcium level was 9.5 mg/dL (Figure 1). At discharge, the patient was advised to discontinue use of cholecalciferol and calcium supplements except for the small doses present in her multivitamin. Studies were performed again 1½ months after discontinuation of use of cholecalciferol and calcium supplementation. At this time, her serum calcium level was 9.8 mg/dL, ionized calcium level was 5.16 mg/dL, 25-OH D level was 59 ng/mL, PTH level was less than 1 ng/L, and 1,25-dihydroxyvitamin D level was 31 pg/mL (reference range, 18-72 pg/mL; to convert to picomoles per liter, multiply by 2.6).

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-
ciferol of 10,000 IU daily.10,14 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.15,16

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.

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