Vitamin D Toxicity due to a Commonly Available “Over the Counter” Remedy from the Dominican Republic

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Context: Hypercalcemia in ambulatory patients is occasionally caused by vitamin D toxicity.

Objective: We report nine patients presenting to Columbia University Medical Center with hypercalcemia due to a supplement from the Dominican Republic containing massive amounts of vitamin D.

Methods: Case histories and laboratory evaluation (calcium, PTH, vitamin D metabolites) are discussed in the context of other published cases of vitamin D toxicity. The supplement was analyzed by HPLC to quantitate vitamin D and A content.

Results: Nine patients presented with hypercalcemia (range, 10.8–17.2 mg/dl; normal, 8.4–9.8 mg/dl), suppressed PTH (range, <3 to 11 pg/ml), and elevated 25-hydroxyvitamin D (range, 94–525 ng/ml; normal, 30–80 ng/ml) levels. All reported recently taking an over-the-counter vitamin supplement called Soladek readily available in the Dominican Republic and in Upper Manhattan. Although serum calcium values before the ingestion of Soladek were not elevated (baseline serum calcium range, 8.7–9.2 mg/dl), most had a disorder that can be associated with hypercalcemia [squamous cell cancer (n = 1), *Pneumocystis* or mycobacterial infection (n = 3), lymphoma (n = 1), granulomatous disease (n = 1), hyperthyroidism (n = 2)]. According to the manufacturer’s label, each 5-ml vial of Soladek contains vitamin D (600,000 IU), vitamin A (120,000 IU), and vitamin E (5 mg). Laboratory analysis by HPLC revealed that the supplement actually contained vitamin D₃ (864,000 IU) and vitamin A (predominantly retinyl palmitate 123,500 IU) per vial.

Conclusion: Although hypercalcemia due to exogenous use of vitamin D is unusual, it is important to consider it in the differential diagnosis, particularly among individuals with access to Soladek. (*J Clin Endocrinol Metab* 96: 291–295, 2011)
Measurements of serum calcium were made by autoanalyzer methods. PTH was measured by immunoradiometric assay (Siemens Medical Solutions, Malvern, PA). 25-Hydroxyvitamin D [25(\OH)D] was measured by chemiluminescent immunoassay (DiaSorin Liaison; ARUP Laboratories, Salt Lake City, UT) and 1,25-dihydroxyvitamin D [1,25(\OH)2D] was measured by RIA (ARUP Laboratories).

Case reports

Case 1
A 35-yr-old woman was admitted with asymptomatic hypercalcemia of 13.5 mg/dl 9 months after diagnosis with stage IIb cervical squamous cell carcinoma. She reported drinking three to four “health tonics” rich in calcium and several servings of milk and calcium-fortified orange juice daily. Estimated calcium intake from this regimen was 3.5 g/d. She also reported taking a daily liquid vitamin preparation she thought contained a vitamin B complex. PTH was undetectable (<3 pg/ml); 25(\OH)D was markedly elevated (288 ng/ml; normal, 30–80 ng/ml). 1,25(\OH)2D was 172 pg/ml (normal, 15–75 pg/ml), and PTHrP was 5.1 pmol/liter (normal, 0–1.5 pmol/liter).

The patient later reported having taken several doses (5 ml every 2 wk for 2 months) of Soladek (Indo-Pharma, Santo Domingo, Dominican Republic), an over-the-counter preparation. The manufacturer’s label stated that it contains vitamin D (600,000 IU), vitamin A (120,000 IU), and vitamin E (5 mg) per 5 ml. The patient was treated with iv fluids and a bisphosphonate. The hypercalcemia resolved and did not recur.

Case 2
A 51-yr-old man with newly diagnosed HIV was admitted with 3 months of weight loss, fevers, night sweats, malaise, and productive cough. Physical examination showed tachycardia, temporal wasting, and diffuse lymphadenopathy. The serum calcium concentration was 15.3 mg/dl, albumin was 3.1 g/dl, and creatinine was 3.5 mg/dl. The patient was found to have active pulmonary Mycobacterium bovis with multiple opacities on chest x-ray. Serum PTH and PTHrP levels were undetectable, 25(\OH)D was 85 ng/ml, and 1,25(\OH)2D was 162 pg/ml. Serum calcium stabilized in the low-mid 11-mg/dl range after a course of antitubercular therapy, iv fluids, and glucocorticoids. He was readmitted 18 months later with recurrent Mycobacterium bovis. Serum calcium was 17.1 mg/dl, PTH and PTHrP were undetectable, 25(\OH)D was markedly elevated at 525 ng/ml, and 1,25(\OH)2D was above 180 pg/ml. A history of recent Soladek use was obtained upon further questioning.

Case 3
A 61-yr-old woman with sarcoidosis (pulmonary, eye, joint, liver, and rectum) was admitted with a serum calcium of 17.2 mg/dl. Outpatient medications included hydrochlorothiazide, methotrexate, folic acid, pantoprazole, metoprolol, aspirin, and calcium supplements. PTH level was undetectable, 25(\OH)D was 94 ng/ml, and 1,25(\OH)2D was 173 pg/ml. There was no evidence of active sarcoidosis. TSH (0.16 \muU/ml) was suppressed. A nodular goiter with low 123I uptake was consistent with thyroiditis. The patient reported taking several vials of Soladek in the month before admission.

Case 4
A 92-yr-old woman with a history of lethargy, weakness, falls, and urinary incontinence was found to have hypercalcemia to 14.7 mg/dl. Her medications included: aspirin, hydrochlorothiazide/losartan, metoprolol, isosorbide mononitrate, furosemide, gingko, coenzyme Q10, vitamin B complex, and corticosteroids. PTH level was 7 pg/ml, 25(\OH)D was 370 ng/ml, and 1,25(\OH)2D was 39 pg/ml. Serum and urine protein electrophoretic profiles were normal. TSH was suppressed (0.17 \muU/ml). A nodular goiter with low 123I uptake was consistent with thyroiditis. The patient admitted to recently taking Soladek.

Case 5
A 34-yr-old man with a 2-yr history of HIV, on no antiretroviral medications, complained of dyspnea, cough, fevers, and chills. Serum calcium was 12.8 mg/dl. PTH level was undetectable, 25(\OH)D was 295 ng/ml, and 1,25(\OH)2D was 72 pg/ml. Bronchoscopy revealed Pneumocystis carinii. Studies for acid fast bacilli, toxoplasma, histoplasma, cryptococcus, human T-lymphotrophic virus, cytomegalovirus, and rapid plasma reagin were negative. The patient stated that he had been taking various vitamins, including Soladek.

Case 6
A 40-yr-old woman with a 2-yr history of HIV presented with 6 wk of fever, cough, weight loss, increasing abdominal girth, lower extremity edema, and early satiety. Serum calcium was 14.8 mg/dl, PTH was undetectable, 25(\OH)D was 184 ng/ml, 1,25(\OH)2D was above 200 pg/ml, and PTHrP was undetectable. Liver biopsy revealed diffuse large B-cell lymphoma. Studies for human T-lymphotrophic virus, \alpha-fetoprotein, carcinoembryonic antigen, and cancer antigen 19-9 were negative; cancer antigen 125 level was 1100 U/ml (normal range, 0–35 U/ml). Further history revealed that the patient had taken Soladek for several weeks before admission.

Case 7
A 71-yr-old woman was admitted to the hospital with fatigue and lethargy. She was found to be in renal failure (serum creatinine, 5.5 mg/dl) and to have new onset hypercalcemia to 15.0 mg/dl. She had been taking calcium supplements (one tablet three times daily), alendronate, hydrochlorothiazide, atenolol, losinopril, and ibuprofen. Evaluation revealed that PTH level was 11 pg/ml, 25(\OH)D was 154 ng/ml, 1,25(\OH)2D was 181 pg/ml, serum protein electrophoresis and urine protein electrophoresis were normal, and thyroid function tests were normal. The patient stated that she had taken a dose of Soladek 2 wk before admission. Her renal failure was presumed to be due to hypercalcemia because the urine sediment and renal ultrasound were unremarkable. Serum creatinine improved with iv fluids.

Case 8
A 42-yr-old woman was evaluated for hypercalcemia to 10.8 mg/dl. She was taking levothyroxine, propranolol, paroxetine, and ibuprofen. The physical examination was unremarkable. The TSH level was 0.28 \muU/ml, PTH was undetectable, PTHrP was undetectable, 25(\OH)D was 119 ng/ml, and 1,25(\OH)2D was 113 pg/ml. Further history revealed that she had taken Soladek twice over several months preceding her clinic visit. After discontinuation of Soladek, the vitamin D and calcium levels normalized over several months.
Case 9

A 43-yr-old female with a 10-yr history of HIV, who progressed to AIDS and was on no antiretroviral medications, presented with a 2-d history of vomiting and diarrhea in the setting of several weeks of subjective fevers, chills, and 40-pound unintentional weight loss. Her serum calcium was 13.4 mg/dl on admission. The PTH level was undetectable, PTHrP was not elevated, 25(OH)D was 194 ng/ml, and 1,25(OH)2D was 118 pg/ml. The patient was diagnosed with disseminated Mycobacterium avian complex and was treated with antimycobacterial therapy. She reported taking Soladek.

Results

All patients were treated with iv or oral hydration, and all but two received a bisphosphonate and/or glucocorticoid therapy, with subsequent normalization of the serum calcium and a substantial decrease in vitamin D levels over weeks to months (Table 1 and Fig. 1). In no case was recurrent hypercalcemia observed after stopping the Soladek and normalization of the serum calcium.

We purchased two 5-ml vials of Soladek from the same lot at a Dominican market in New York City. It was routinely available in Washington Heights, a Hispanic neighborhood in northern Manhattan. We analyzed the two vials for 25(OH)D, 1,25(OH)2D, parent vitamin D, and vitamin A by HPLC. Each vial contained approximately the amount of vitamin A (predominantly retinyl palmitate) as the package insert specified (123,500 IU). However, each vial contained substantially more vitamin D (in the cholecalciferol form) than claimed, namely 864,000 IU. There was no measurable 25(OH)D or 1,25(OH)2D in the preparation. These amounts of vitamin D and vitamin A are 400 and 12 times greater, respectively, than the currently accepted tolerable upper intake levels of these vitamins as recommended by the Food and Nutrition Board of the Institute of Medicine (1).

Discussion

This report calls attention to Soladek, an over-the-counter preparation readily available in the Dominican Republic, a Hispanic neighborhood in New York City, and presumably many other parts of the United States. In the dosage recommended in the package insert, it contains large amounts of vitamins D and A. Each subject of this report had another potential cause for hypercalcemia, but in no case had the patient experienced hypercalcemia before ingesting Soladek. A role that the underlying condition might have played in contributing to the hypercalcemia is plausible but

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**TABLE 1. Biochemical features on admission and follow-up**

<table>
<thead>
<tr>
<th>Case</th>
<th>Ca (mg/dl)</th>
<th>F/U Ca</th>
<th>PTH (ng/ml)</th>
<th>25D (ng/ml)</th>
<th>1,25D (pg/ml)</th>
<th>F/U Alk phos (U/liter)</th>
<th>PTHrP (pmol/liter or pmol/ml)</th>
<th>BUN/Cr (mg/dl)</th>
<th>Alk phos (U/liter)</th>
<th>Other conditions</th>
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<td>1</td>
<td>13.5</td>
<td>9.5</td>
<td>&lt;3</td>
<td>288</td>
<td>69</td>
<td>172</td>
<td>55</td>
<td>15/1.0</td>
<td>14–27 pg/ml</td>
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<tr>
<td>2</td>
<td>17.1</td>
<td>9.9</td>
<td>&lt;3</td>
<td>525</td>
<td>86</td>
<td>&gt;180</td>
<td>78</td>
<td>U</td>
<td>32/1.8</td>
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<td>3</td>
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<td>9.7</td>
<td>&lt;3</td>
<td>94</td>
<td>54</td>
<td>173</td>
<td>U</td>
<td>32/1.5</td>
<td>68/3.2</td>
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<td>9.3</td>
<td>7</td>
<td>370</td>
<td>39</td>
<td></td>
<td></td>
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<td>28/1.5</td>
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<tr>
<td>5</td>
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<td>9.8</td>
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<td>295</td>
<td>72</td>
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<td>24/1.3</td>
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<td>9.2</td>
<td>&lt;3</td>
<td>184</td>
<td>84</td>
<td>&gt;200</td>
<td>140</td>
<td>U</td>
<td>54/5.5</td>
<td>HCTZ</td>
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<tr>
<td>7</td>
<td>15.0</td>
<td>10.2</td>
<td>11</td>
<td>154</td>
<td>85</td>
<td>181</td>
<td>141</td>
<td>U</td>
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<td>10.8</td>
<td>9.4</td>
<td>&lt;3</td>
<td>119</td>
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<td>113</td>
<td>74</td>
<td>12</td>
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<tr>
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<td>12.6</td>
<td>9.2</td>
<td>&lt;3</td>
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<td>118</td>
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</table>

25D, 25(OH)D; 1,25D, 1,25(OH)2D; Alk phos, alkaline phosphatase; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; F/U, follow-up, generally 2 to 12 wk after initial presentation; HCTZ, hydrochlorothiazide; MAI, mycobacterium avium-intracellulare; U, undetectable.

* Mean follow-up time, 6.5 ± 1.6 (sem) wk.

To convert calcium from mg/dl to mmol/liter, multiply by 0.25.

To convert 25(OH)D from ng/ml to nmol/liter, multiply by 2.496.

To convert 1,25(OH)2D from pg/ml to pmol/liter, multiply by 2.6.

Normal range of PTHrP was 0–1.5 pmol/liter for cases 1–8, and 14–27 pg/ml for case 9.

To convert blood urea nitrogen from mg/dl to mmol/liter, multiply by 0.357; to convert creatinine from mg/dl to μmol/liter, multiply by 88.4.
not clear. In the patients we describe, hypercalcemia did not recur after Soladek was discontinued. A logical explanation is that the underlying condition was a contributing factor but not sufficient by itself to cause hypercalcemia.

The package label for Soladek lists the following indications for its use: “hypo and avitaminosis, rickets, growth, dentition, lactation, fractures, infections, convalescence, protection and regeneration of certain epithelium (bronchial, glandular, ocular, cutaneous), corticotherapy, aging, and pregnancy.” The package insert also states that there are no contraindications or medicine interactions, although listed secondary effects are “nausea, anorexia, migraines, and polyuria.” It is our understanding that this preparation is commonly used in the Dominican Republic as a homeopathic remedy for prevention and treatment of any general illness.

In uncomplicated vitamin D toxicity due to ingestion of parent vitamin D (cholecalciferol or ergocalciferol), 25(OH)D is often present in pharmacologically active amounts with normal serum 1,25(OH)2D levels (2, 3). The liver converts almost all vitamin D to 25(OH)D through the action of a number of loosely regulated substrate-dependent cytochrome P450-linked oxidases (4). 25(OH)D, the hepatic product, therefore, usually reflects the amount of parent vitamin D. It is likely that in cases of vitamin D toxicity, such as those reported in this study, it is the 25(OH)D that is responsible for the hypercalcemia. At high concentrations, vitamin D metabolites such as 25(OH)D may compete for binding at vitamin D receptor sites, thereby producing effects similar to those of 1,25(OH)2D by initiating translation of vitamin D receptor-responsive genes (5). In addition, high concentrations of 25(OH)D may also saturate the vitamin D binding protein, resulting in its greater availability at tissue sites (2, 3, 6). Most of the cases in this series can thus be explained by the vitamin D in the Soladek preparation being converted to excessively high levels of 25(OH)D. In most of the cases reported, 1,25(OH)2D was unlikely to be a major factor because the renal 1α-hydroxylase enzyme is under strict control and often limits the production of 1,25(OH)2D, even if large amounts of 25(OH)D are available. In fact, the ratio of serum 25(OH)D/1,25(OH)2D in ng/ml and pg/ml, respectively, exceeded one in six of our nine cases. In addition to the kidney, however, a number of other tissues express 1α-hydroxylase, and local paracrine conversion of 25(OH)D to 1,25(OH)2D may also have contributed to the hypercalcemia. This is particularly likely in inflammatory states in which macrophages and other cells with this enzymatic competence locally convert 25(OH)D to 1,25(OH)2D (7–14). In the cases reported here where levels of 1,25(OH)2D were elevated, “spill over” of this locally produced metabolite into the circulation could have occurred.

Specific situations in some of the cases are noteworthy. For example, in case 1, local production of PTHrP could have accelerated conversion to 1,25(OH)2D, although in cases of PTHrP-associated hypercalcemia, 1,25(OH)2D levels are typically suppressed. In the patient with sarcoidosis (case 3), the elevated 1,25(OH)D could have been due to 1α-hydroxylase activity from granulomatous tissue. In the patients with HIV disease and associated Pneumocystis carinii or mycobacterium infection (cases 2, 5, and 9), hypercalcemia with elevated 1,25(OH)2D levels has been described (7–12). The literature reports hypercalcemia in association with Mycobacterium avium, but not with Mycobacterium bovis. In the patient with lymphoma, production of 1,25(OH)2D by activated macrophages has been described (12–14) and could have contributed to cause hypercalcemia. In the other patients, the concomitant use of thiazide diuretic therapy (cases 3, 4, and 7) or the overuse of thyroid hormone (case 8) could have contributed to the hypercalcemia (15–17).

Hypercalcemia due to excess ingestion of vitamin D in dietary supplements has been reported previously (18–20). In two cases, the amounts of vitamin D found in vitamin preparations were much higher than listed by the manufacturer (19, 20). The inadvertent overfortification of milk has also been reported to cause vitamin D toxicity (21, 22).

We are aware of only two case reports in the literature describing hypercalcemia with Soladek use. One is an abstract of a 4-yr-old boy given Soladek who presented with hypercalcemia to 18.9 mg/dl; he was otherwise healthy on no medications (23). Leu et al. (24) describe a 60-yr-old woman presenting with symptoms of hypercalcemia and a serum calcium level of 15.2 ng/dl. Her 25(OH)D level was above 150 ng/ml with undetectable PTH and PTHrP. Computed tomography of the torso, skeletal survey, and bone marrow biopsy were negative for malignancy; however, colonoscopy revealed an anal squamous cell carcinoma. The hypercalcemia resolved after discontinuation of Soladek in addition to treatment with iv fluids and a bisphosphonate (24).

Sanders et al. (25) performed a placebo-controlled, double-blind study of cholecalciferol 500,000 IU annually in 2256 ambulatory women aged 70 yr or older. They found a 15% increase in falls and a 26% increase in fractures in the treatment group. In the biochemical substudy, the highest 25(OH)D level 1 month after treatment was 83 ng/ml; serum calcium was not obtained. This paper demonstrates that high-dose vitamin D supplementation can cause some toxicity at serum 25(OH)D values that are not frankly elevated, with the caveat that earlier 25(OH)D values are unavailable.

Vitamin A toxicity is a rare but well-documented cause of hypercalcemia (26). The mechanism remains unknown, however, likely due to excessive bone resorption (27). Vi-
tamin A toxicity could also have been an important contributing factor in the hypercalcemia reported here and could account for the mild liver function abnormalities seen in several cases.

It is reasonable to presume that Soladek use in these cases was the major cause of the hypercalcemia. Because this preparation is readily available in the Dominican Republic and in many Hispanic regions of the United States, vitamin D toxicity must be considered in the differential diagnosis of hypercalcemia among subjects who have recently been abroad or who have access to this supplement.

This report also underscores the point that when patients who harbor a condition that can be associated with hypercalcemia become hypercalcemic, the hypercalcemia may not necessarily be due to the underlying condition but rather to a different etiology. In special situations, such as those described here, the physician should consider other etiologies to account for the hypercalcemia.

Conclusion

This series of nine patients with hypercalcemia emphasizes the increasing availability of a potent over-the-counter vitamin D preparation that contains large amounts of vitamin D. In patients who present with hypercalcemia and have access to Soladek, this potential etiology should be considered, even if there is another apparent cause for the hypercalcemia.

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