Vitamin D Intoxication Due to an Erroneously Manufactured Dietary Supplement in Seven Children

abstract

Pediatric cases of vitamin D intoxication (VDI) with dietary supplements have not been previously reported. We report on 7 children with VDI caused by consumption of a fish oil supplement containing an excessively high dose of vitamin D due to a manufacturing error. Seven children aged between 0.7 and 4.2 years were admitted with symptoms of hypercalcemia. Initial median (range) serum concentrations of calcium and 25-hydroxyvitamin D were 16.5 (13.4–18.8) mg/dL and 620 (340–962) ng/mL, respectively. Repeated questioning of the parents revealed use of a fish oil that was produced recently by a local manufacturer. Analysis of the fish oil by gas chromatography/mass spectrometry revealed that the vitamin D3 content was ∼4000 times the labeled concentration. Estimated daily amounts of vitamin D3 intake varied between 266,000 and 800,000 IU. Patients were successfully treated with intravenous hydration, furosemide, and pamidronate infusions. With treatment, serum calcium returned to the normal range within 3 days (range: 2–7 days). Serum 25-hydroxyvitamin D levels normalized within 2 to 3 months. Complications, including nephrocalcinosis, were not observed throughout the 1-year follow-up. In conclusion, errors in manufacturing of dietary supplements may be a cause of VDI in children. Physicians should be aware of this possibility in unexplained VDI cases and repeatedly question the families about dietary supplement use. To prevent the occurrence of such unintentional incidents, manufacturers must always monitor the levels of ingredients of their products and should be rigorously overseen by governmental regulatory agencies, as is done in the pharmaceutical industry. Pediatrics 2014;133:e1–e5
Vitamin D intoxication (VDI) is a rare condition today. Over the past 40 years, it has been usually described as a result of unintentional conditions, such as contamination of cooking oil,1–3 over-fortification of milk,4,5 or adulteration of table sugar6 VDI associated with over-the-counter dietary supplements has been reported in adult patients.7–12 However, to our knowledge, pediatric cases of VDI caused by dietary supplements have not been previously reported. We report here on 7 young children with VDI caused by the consumption of a fish oil supplement that contained an excessively high dose of vitamin D due to a manufacturing error.

CASE HISTORIES

A 2.5-year-old boy was admitted on September 24, 2011, with a history of fever, weakness, constipation, loss of appetite, nausea, and vomiting for 2 weeks. He was clinically dehydrated. His serum calcium and 25-hydroxyvitamin D (25(OH)D) levels were 16.6 mg/dL and 340 ng/mL, respectively. His physical examination was normal. His serum calcium and 25-hydroxyvitamin D (25(OH)D) levels were 13.4 mg/dL (normal range: 8.8–10.8 mg/dL) and 962 ng/mL (normal range: 30–80 ng/mL), respectively. His parents denied taking any drug or dietary supplement containing vitamin D.

On the third day of the second child’s admission, a 21-month-old girl was admitted with a chief complaint of severe leg pain. In addition, she had loss of appetite, vomiting, constipation, polydipsia, and polyuria for 3 days. She appeared weak and dehydrated and could not stand on her feet due to leg pain. Laboratory studies revealed very high levels of serum calcium (18.8 mg/dL) and 25(OH)D (736 ng/mL). Her family affirmed that the child had been taking the same fish oil for the past 20 days.

During this period, we again questioned the first family and found out that they had used the same product for 2 months before the onset of symptoms. Thus, all 3 patients with unexplained VDI had similar medical histories. Their symptoms of hypercalcemia had emerged after consumption of the fish oil. This nutritional supplement had been manufactured recently by a local company, with permission of the Ministry of Food and Agriculture (registration date: April 19, 2011; no. G-55-1147). We reported these 3 cases to the Provincial Directorates of Health and Agriculture and also informed them about the product that was identified as the common exposure among the affected children. Upon this alert, the manufacturer recalled 1000 bottles of the product in a few days. However, 4 new patients, whose ages ranged from 0.7 to 4.2 years, presented in the subsequent 3 weeks between October 12 and November 1 with similar medical histories and clinical and laboratory findings (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Number</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D, ng/mL</td>
<td>1</td>
<td>962</td>
</tr>
<tr>
<td>Ca, mg/dL</td>
<td>1</td>
<td>13.4</td>
</tr>
<tr>
<td>P, mg/dL</td>
<td>1</td>
<td>5.10</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>Cre, mg/dL</td>
<td>1</td>
<td>0.77</td>
</tr>
<tr>
<td>UCa/Cre, mg/mg</td>
<td>1</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Ca, calcium; Cre, creatinine; ND, not done; P, phosphorus; PTH, parathyroid hormone; UCa/Cre, urinary calcium:creatinine ratio.

* Normal ranges: 25(OH)D, 30–80 ng/mL; Ca, 8.8–10.8 mg/dL; P, 5.1–6.0 mg/dL; for children aged 1 to 4 years; PTH, 15–85 pg/mL; Cre, <0.42 mg/dL for children aged 1 to 4 years; UCa/Cre <0.2 mg/mg.
Five lots of the product provided by the manufacturer were analyzed for vitamin D content by the Research Department of Drug and Cosmetics at the Ministry of Health in Ankara. Analysis by gas chromatography/mass spectrometry revealed that the first lot contained 3.6 mg (144 000 IU) vitamin D₃ per gram of fish oil and that the remaining lots did not contain any vitamin D. The amount of other ingredients within the product, including vitamin A and zinc, was found to be compatible with the labeled quantities. On the basis of the report of the Research Department, we calculated that each 5-mL serving size contained ~20 mg (800 000 IU) vitamin D₂. This amount was 4000 times the labeled concentration. Thus, analysis of the fish oil confirmed an error in manufacturing of the product. The patients had consumed 0.5 to 2 bottles of fish oil from the first lot over a period of 15 to 60 days. The estimated daily vitamin D₂ intake varied between 266 000 and 800 000 IU. These doses were 177 to 320 times the recommended tolerable upper limits for infants and children (Table 2).¹³

The patients received a calcium- and vitamin D-restricted diet until all laboratory variables returned to normal. All patients were treated with intravenous hydration (1.5 to 2 times the daily maintenance dose), furosemide (1–2 mg/kg per day), and pamidronate (1 mg/kg per dose). The median duration of therapy was 4 (2–7) days. Prednisolone was used only for treatment of the first patient. In this single patient, initial serum calcium increased to a higher level under treatment (Fig 1). Upon failure of therapy with prednisolone, an infusion of pamidronate was administered. In the other 6 patients, pamidronate was used as the first-line therapy. One or two doses of pamidronate effectively lowered serum calcium levels to the normal range within a median duration of 3 days (range: 2–5 days).

The patients’ laboratory data are shown in Table 1 and Fig 1. Serum 25(OH)D levels decreased gradually and returned to normal within 2 to 3 months (Fig 1A). With treatment, serum calcium levels normalized within 2 to 7 days (Fig 1B). During the period during which serum 25(OH)D levels were persistently high, hypercalcemia did not recur. Initial serum phosphorus levels were within normal limits for the age group (Table 1). In the first week of bisphosphonate treatment, both serum phosphorus and calcium levels decreased in all patients. In 5 patients, phosphorus levels decreased to the hypophosphatemic range. Serum creatinine levels at time of presentation were elevated in all but one of the patients, and serum phosphorus and creatinine levels recovered in the second week. The urinary calcium:creatinine ratio decreased markedly within 2 weeks and remained at normal limits in 4 patients. However, 3 patients developed persistent hypercalciuria despite normocalcemia (Table 1). These patients’ urinary calcium excretion reverted to the normal range in the fourth month of follow-up. Initial ultrasound examinations revealed mildly increased echogenicity of the renal medulla in 2 patients, indicating medullary nephrocalcinosis. However, repeated ultrasound images were normal at months 6 and 12. Thus, no patient developed nephrocalcinosis or any other sequelae throughout the 1-year follow-up.

**LABORATORY METHODS**

The concentration of vitamin D₃ in the dietary supplement was determined by gas chromatography/mass spectrometry. Serum 25(OH)D levels were measured by high-performance liquid chromatography. Serum and urinary levels of calcium, phosphorus, and creatinine were measured by colorimetric and spectrophotometric methods by using the Roche Cobas 8000 modular analyzer. Serum parathyroid levels were measured by

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**TABLE 2 Estimated Amount of Vitamin D₃ Ingested by the Children**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gender</th>
<th>Age, y</th>
<th>Body Weight, kg</th>
<th>Period, d</th>
<th>Estimated Amount of Vitamin D₃ Ingested</th>
<th>UL of Vitamin D, IU/d</th>
<th>Ingested Amount: UL Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total, mg³</td>
<td>Average per Day</td>
<td>mg/kg</td>
</tr>
<tr>
<td>1</td>
<td>Male</td>
<td>2.5</td>
<td>10.0</td>
<td>60</td>
<td>800</td>
<td>1.33</td>
<td>533 000</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>1.1</td>
<td>11.5</td>
<td>15</td>
<td>285</td>
<td>1.54</td>
<td>707 000</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>1.7</td>
<td>12.7</td>
<td>20</td>
<td>400</td>
<td>1.57</td>
<td>800 000</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>3.2</td>
<td>13.0</td>
<td>18</td>
<td>380</td>
<td>1.54</td>
<td>800 000</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>1.2</td>
<td>9.5</td>
<td>30</td>
<td>600</td>
<td>2.10</td>
<td>800 000</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>4.2</td>
<td>17.0</td>
<td>20</td>
<td>300</td>
<td>0.88</td>
<td>600 000</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>0.7</td>
<td>7.2</td>
<td>30</td>
<td>200</td>
<td>0.92</td>
<td>268 000</td>
</tr>
</tbody>
</table>

Medians (range): 1.7 (0.7–4.2) 11.5 (7.2–17) 20 (15–60) 360 (200–800) 1.54 (0.88–2.1) 707 000 (266 000–800 000) — 283 (177–320)

³ UL, tolerable upper intake level recommended by the Institute of Medicine and the Endocrine Society (13).

Period of fish oil consumption.

1 mg of vitamin D₃ equals 40 000 IU.
 electrochemiluminescence immunoassay by using the Roche Modular E170 analyzer (Roche Diagnostics, Indianapolis, IN).

**DISCUSSION**

VDI is rarely seen because the therapeutic use of vitamin D at massive doses has been abandoned. But, at present, its incidence appears to be increasing because of the recent increase in dietary supplement use, especially in adults. In recent years, VDI with over-the-counter dietary supplements has been described in adult patients. However, VDI caused by dietary supplements has not been reported in children. Only very recently, Rajakumar et al described an infant who had hypervitaminosis D caused by a dosing error in an over-the-counter vitamin D supplement. They observed that accidental overdosing of the supplement led to elevated 25(OH)D levels without hypercalcemia. Our report defines children with vitamin D toxicity caused by the consumption of an erroneously manufactured, extremely high-dose vitamin D–containing fish oil concentrate.

Although VDI in industrialized countries has been usually associated with food products or dietary supplements, in Turkey it has always resulted from mistakenly used or unnecessary use of high-dose vitamin D-containing ampules. This is the first report, to our knowledge, from Turkey that describes dietary supplement–induced vitamin D toxicity. From this perspective, this unusual incident in 7 young children may be considered as a manifestation and even harbinger of new dangers or troubles that come with the development and industrialization of Turkey. Also, in consideration of the previous case reports, our observation indicates that children living in developed countries are at risk of VDI, which might be caused by the consumption of over-the-counter dietary supplements or remedies.

To prevent the recurrence of these types of incidents, we need to understand why or how this problem occurred. In our incident, the dietary supplement was manufactured and launched just 3 months previously by a small local company founded in 2010. The product was a mixture of fish oil, omega-3 fatty acids, zinc, and 8 vitamins including vitamin D3. The company had been manufacturing the final product in its own factory by mixing ingredients received from suppliers. Human error in the mixing of ingredients resulted in enormously high concentrations of vitamin D in the first lot of the product. Because the content of the final product was not tested before marketing by the company and, more importantly, was not overseen by any governmental regulatory agency, this vital error was not detected. Thus, 7, and possibly more, children were poisoned with vitamin D.

Dietary supplements are considered foods, not drugs, and governmental...
regulations and oversight of dietary supplements and prescription drugs are quite different.24 Before a prescription drug is approved for a disease or condition, it undergoes rigorous review by the regulatory agencies. However, the contents of dietary supplements are not regulated by any agency at this time, and they can vary widely depending on the manufacturer and its standards.25 Consequently, if the fish oil manufacturer, which was new to the field of dietary supplements, had been held to standards used in the pharmaceutical industry and had been rigorously overseen by a governmental regulatory agency, this minor outbreak of vitamin D toxicity might have been prevented. Nevertheless, a much greater outbreak was prevented because the manufacturer immediately recalled the products in the market upon our alert within a relatively short time.

In conclusion, errors in the manufacturing of dietary supplements may be a cause of VDI in children. Parents may not report supplement use. Physicians should be aware of this possibility in cases with unexplained VDI and question repeatedly the families about the consumption of dietary supplements. To prevent the occurrence of such unintentional incidents, the manufacturers must always monitor the levels of ingredients of their products and should be rigorously overseen by governmental regulatory agencies, as is done in the pharmaceutical industry.

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REFERENCES

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