Brief Report

Hypercalcemia due to Hypervitaminosis D: Report of Seven Patients

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Summary

We retrospectively studied seven children (six girls, one boy) aged from 7.5 to 25 months who presented to our institution after taking large doses of vitamin D (900,000–4,000,000 U) prescribed by medical practitioners for wrong indications like failure to thrive, etc. The clinical manifestations were constipation, decreased appetite, lethargy, polyuria, dehydration and failure to thrive. All patients had hypercalcemia (serum calcium ranging from 12 to 16.8 mg/dl), high 25[OH]D levels (ranging from 96 to >150 ng/ml), suppressed intact parathyroid hormone (ranging from <3 to 8.1 pg/ml). Hypercalciuria (urinary calcium/creatinine ranging from 1 to 2.45) was found in all patients, while nephrocalcinosis was present in five patients. All were treated with intravenous fluids, oral prednisolone, restriction of calcium in diet, while four patients received pamidronate infusion for reducing hypercalcemia.

Key words: vitamin D, hypercalcemia, hypervitaminosis.

Vitamin D, a fat-soluble vitamin, is used for the treatment and prevention of rickets. However, overdose leading to hypercalcemia can lead to potential problems. The irrational use of this vitamin is an alarming health care issue in our country. Seven children with vitamin D intoxication (VDI) leading to hypercalcemia are presented here. These children were analysed in terms of doses of vitamin D given, clinical and lab parameters and complications resulting due to VDI.

Material and Methods

Seven children who presented to us over 2 years with hypercalcemia due to hypervitaminosis D were retrospectively studied. Data included age, gender of the patient, dose and duration of vitamin D taken, clinical signs and symptoms, laboratory findings, therapy for VDI and complications. Laboratory investigations included serum calcium (Ca), intact parathyroid hormone (iPTH), 25[OH]D levels, renal function tests, urine analysis and renal ultrasonography (USG).

Results

There were six girls and one boy aged from 7.5 to 25 months who had taken vitamin D in the doses of 900,000–4,000,000 U over a period of 2–8 weeks before presenting to us. Six of these patients were given vitamin D by medical practitioners for indications like failure to thrive, developmental delay and erroneous diagnosis of rickets without supportive investigations. One child had evidence of rickets; however, the parents continued giving vitamin D so as to make the bones strong over and above the prescribed dose by buying vitamin D supplements over the counter.

The clinical manifestations were constipation (n = 1), decreased appetite (n = 2), lethargy (n = 2), hematuria (n = 1), persistent irritability (n = 3), polyuria (n = 5), failure to thrive (n = 4), hypotonia (n = 2), transient hypertension (n = 1) and dehydration (n = 5). The laboratory investigations and renal USG findings are given in Table 1.

As shown in Table 1, all patients had hypercalcemia, hypercalciuria, raised 25[OH]D levels and suppressed PTH levels. Though hypercalciuria was present in all patients, only five had evidence of nephrocalcinosis. Two patients with nephrocalcinosis had high serum creatinine, while three patients had evidence of microscopic hematuria. All patients received treatment with intravenous fluids so as to
rehydrate and increase urinary Ca excretion and oral prednisolone. Three children received pamidronate infusion since there was no appreciable decrease in serum Ca levels; while in one patient, pamidronate was given as there was rebound increase in Ca levels after initial treatment with hydration and prednisolone.

Discussion

The physiological effect of vitamin D in pharmacological doses is to increase gastrointestinal Ca absorption and to increase bone resorption, presumably the high 25[OH]D levels stimulate both the intestinal and bone 1,25 dihydroxy vitamin D receptors [1–3]. Sustained daily intake of 4000 IU in adults and 1800 IU in children has been reported as toxic [4, 5]. Because vitamin D is deposited in adipose tissue [6], hypercalcemia may be persistent leading to complications like nephrocalcinosis. The intake of as little as five times the recommended daily allowance of vitamin D (Recommended Daily Allowance (RDA) = 400 IU) has been associated with toxicity [7]. Our patients had taken 900 000–4 000 000 U of vitamin D, an amount as high as 450–2000 the upper limit of the toxic dose (upper limit = 2000 U) [8].

There have been cases of hypercalcemia due to the consumption of vitamin D-fortified milk [9, 10]. However, in our country VDI is iatrogenic due to the use of high doses of vitamin D as a remedy for delayed development, delayed teething or failure to thrive. Two patients were erroneously diagnosed as having rickets on the basis of clinical signs and given high doses of vitamin D. Though nutritional rickets is a common problem in our country, clinical manifestations may be variable with respect to childhood period in which the diagnosis of rickets is made. The sensitivity, positive predictive value and negative predictive value of physical findings of nutritional rickets were found to be 65.7, 60.9 and 74.6%, respectively, in one study [11]. It can therefore be inferred that physical findings alone in absence of biochemical and radiological investigations are insufficient for prescribing vitamin D and could lead to VDI as had happened in two of our patients.

The typical manifestations of VDI are attributed to the resultant hypercalcemia. These include vomiting, anorexia, constipation, failure to thrive, polyuria, dehydration and fever [12, 13]. We suspected VDI when patients presented with some of the above symptoms. The characteristic laboratory findings of VDI are high serum calcium causing hypercalcuria, low PTH and high 25[OH]D levels, seen in all of our patients. Hypercalcemia leads to nephrocalcinosis by overloading the renal resorptive mechanism. A high calcium load causes damage to cells followed by calcium deposition in tubules, basement membrane and loop of Henle [2, 14]. Three patients had nephrocalcinosis at presentation, while two patients developed it during treatment. Vitamin D toxicity has been seen as one of the important but uncommon causes of iatrogenic nephrocalcinosis. In a retrospective survey of 152 children and adolescents with nephrocalcinosis, prophylactic administration of vitamin D was found to cause nephrocalcinosis in 9% cases [15]. Resolution of nephrocalcinosis has not been well documented. In one study, none of the five children with vitamin D-induced nephrocalcinosis showed resolution over the years [16]. A follow-up of 12–15 months in our patients showed persistence of nephrocalcinosis in all.

The therapy of VDI-related hypercalcemia was instituted in all our patients in the form of hydration, oral prednisolone, diet containing low Ca and discontinuation of vitamin D. Another effective modality is use of bisphosphonates especially the pamidronate. It inhibits osteoclast-mediated bone resorption causing a brisk reduction of serum calcium even when therapy with hydration and prednisolone has not produced significant effect [17, 18]. We treated four of our patients with pamidronate infusion at 1 mg kg$^{-1}$ dose$^{-1}$, three of whom required repeated infusion to control hypercalcemia.

<table>
<thead>
<tr>
<th>No.</th>
<th>Serum Ca (mg dl$^{-1}$)</th>
<th>25[OH]D levels (ng ml$^{-1}$)</th>
<th>iPTH (pg ml$^{-1}$)</th>
<th>Urine Ca/Cr</th>
<th>Renal USG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>&gt;150</td>
<td>&lt;3</td>
<td>2.3</td>
<td>Nephrocalcinosis</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>&gt;150</td>
<td>7.7</td>
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<td>Nephrocalcinosis</td>
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<tr>
<td>3</td>
<td>13.9</td>
<td>&gt;100</td>
<td>&lt;3</td>
<td>1.27</td>
<td>Nephrocalcinosis</td>
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<tr>
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<td>15.1</td>
<td>&gt;150</td>
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<td>5</td>
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<td>6</td>
<td>12.9</td>
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<td>7</td>
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Normal laboratory values: 25[OH]D, 25–45 ng ml$^{-1}$; iPTH, 9–65 pg ml$^{-1}$.
In conclusion, there should be an increased awareness of the potential seriousness of the problem among the medical practitioners who prescribe vitamin D for wrong reasons, so as to decrease the morbidity from VDI. Vitamin D should be prescribed for suspected rickets only after proper investigations. Parents should be clearly advised against unsupervised or un-prescribed supplements of vitamin D. The possible toxic effects should also be explained to them. Prohibiting over the counter sale of vitamin D will also help prevent drug consumption without prescription.

References


