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Case Report

Vitamin D Intoxication Caused by a Manufacturing Error in a Prescribed Vitamin D3 Supplement, Successfully Managed with Low-Dose Zoledronic Acid

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Abstract: We describe a 3.5-year-old boy with a history of operated posterior urethral valves and a single functioning kidney, who developed vitamin D toxicity with hypercalcemia after he was prescribed orally 6,000 IU of cholecalciferol daily for two months for vitamin D deficiency. The disordered calcium metabolism was discovered during hospitalization for a urinary tract infection, along with evidence of renal failure (serum creatinine 1.63 mg/dL). Serum calcium on admission was 16.91 mg/dL. The measured 25(OH)D level was extremely high (3,555 ng/mL), along with a low serum parathyroid hormone (3.3 pg/mL), suggestive of severe vitamin D overdose. Hypercalcemia was initially managed with discontinuation of oral vitamin D supplementation, aggressive intravenous hydration, administration of corticosteroids, and a low calcium diet, but the serum calcium remained elevated (13.3 mg/dL), 8 days after hospital admission. At that point, and since the patient's renal function had substantially improved (serum creatinine 0.71 mg/dL), he received a single dose of zoledronic acid 0.03 mg/kg. The hypercalcemia resolved within two days and did not recur. It was later discovered that the patient had been receiving daily for the last two months an oral solution of vitamin D3 that was recalled due to a higher content of vitamin D3 than stated on its label. Any child presenting with hypercalcemia and low parathyroid hormone should be investigated for the possibility of vitamin D toxicity. Therapy with low-dose bisphosphonates is effective in cases of symptomatic hypercalcemia that does not completely respond to other therapeutic maneuvers, provided that the patient has adequate renal function.

Keywords: Vitamin D Intoxication; Hypercalcemia; Parathyroid Hormone; Rickets; Zoledronic Acid.

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1. Introduction

Vitamin D is an essential fat-soluble vitamin made in humans after exposure of the skin to sunlight [1]. It is also found in various animal products and fortified foods. The best way to maintain adequate vitamin D intake is through supplemental vitamin D, such as oral ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) [2]. Vitamin D is essential for bone health, and its deficiency can lead to rickets and osteopenia. Countries of the northern hemisphere recommend universal vitamin D supplementation in infants, toddlers, and adolescents to optimize 25-hydroxy-vitamin D [25(OH)D] serum levels and prevent nutritional rickets. Oral calcium, 500 mg/day, either through diet or supplements,

should be routinely used together with vitamin D to prevent nutritional rickets [3]. Hypervitaminosis D or vitamin D intoxication is rare and usually caused by excessive consumption of vitamin D, either due to misuse of over-the-counter supplements, inaccurate medical prescriptions, or use of products that contain more vitamin D3 than written on the label [4].

2. Case Report

A phenotypically normal 3.5-year-old boy was admitted to our hospital for a urinary tract infection (UTI) along with evidence of renal failure. Two days ago, he started having spiking fevers up to 39.8°C and decreased oral intake, for which a urine culture was obtained that grew *Escherichia coli*, sensitive to co-amoxiclav, which he began empirically by mouth before the results of the urine culture were available.

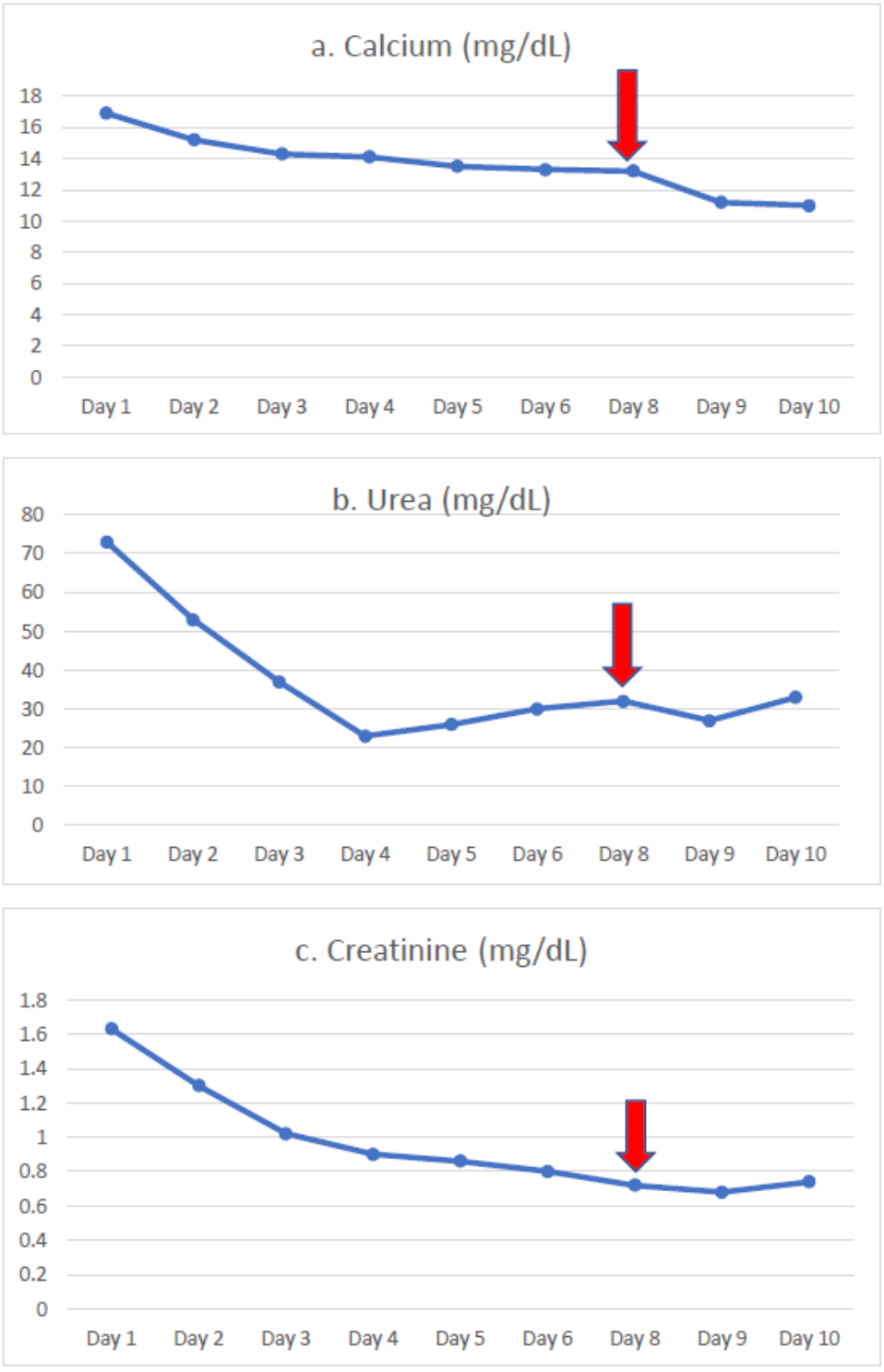
The patient was born and lived in the United Kingdom, and he was visiting Greece for summer vacation. His medical history was remarkable for the presence of posterior urethral valves, for which he was operated on in the third week of life and again at the age of 6 months. Hs was undergoing clean intermittent catheterization 5-6 times daily and was receiving oral nitrofurantoin chemoprophylaxis for recurrent UTIs, along with oral oxybutynin and sodium feredetate. Two months ago, he was started on cholecalciferol, 6,000 IU per os daily, apparently for a serum 25(OH)D concentration of 32 nmol/L (=12.8 ng/mL), and the perceived increased risk for rickets due to his non-functioning left kidney. Notably, at that time, he did not have any clinical signs or symptoms of rickets, and he had a normal serum calcium by parental report. The product he received (Aactive D3® oral solution, TriOn Pharma) was labeled to have a concentration of vitamin D3 2,000 IU/mL, and the family followed exactly the written order of their physician in the United Kingdom. Since the supplement was given daily by the mother and was kept in a safe place, there was no possibility of child-induced accidental overdose.

Physical examination on admission showed a thin, dehydrated, and drowsy child in no apparent distress with good vital signs. Laboratory work-up showed leukocytes 9,840/μL, hemoglobin 11.7 g/dL, hematocrit 32.7%, platelets 282,000/μL, increased serum C-reactive protein (7.5 mg/dL, normal <0.5), along with an elevated serum creatinine 1.63 mg/dL (reference range for age 0.29-0.7) and urea 73 mg/dL(reference range for age 11-36), as well as high serum calcium 16.91 mg/dL (reference range 8.8-10.8) with high ionized calcium 9.06 mg/dL (reference range 4.8-5.5). The patient's urinalysis showed 50 leukocytes/HPF, while the urine culture was negative for bacterial growth. The calcium to creatinine ratio on a spot urine sample was elevated at 0.74 (normal for age <0.2). The intact parathyroid hormone (PTH) serum concentration was low at 3.3 pg/mL (reference range 9-52), while the measured 25(OH)D was extremely high at 3,555 ng/mL (reference range 50-80). The measurement of 25(OH)D was done with the Elecsys Vitamin D total III assay (Roche Diagnostics GmbH, Mannheim, Germany), an electrochemiluminescence binding assay for use on cobas e immunoassay analyzers. The measuring range of 25(OH)D in this assay is 6-120 ng/mL, and appropriate dilutions were required to determine the correct serum concentration. The reported value of 25(OH)D was confirmed twice.

A urinary catheter was introduced and left in place to accurately record the daily urine output, while intravenous ceftriaxone was prescribed to continue treatment of the UTI. Due to the compromised renal function and the accompanying hypercalcemia, the patient was aggressively hydrated with normal saline, while intravenous methylprednisolone at 1 mg/kg daily, divided into two doses, was started to decrease the formation of 1,25(OH)2D and the absorption of dietary calcium. Despite the immediate discontinuation of supplemental vitamin D, receiving a low-calcium diet, and paying meticulous attention to his fluid balance, the serum calcium continued to be elevated at 13.3 mg/dL on the 8th hospital day. At that point, a single dose of zoledronic acid 0.5 mg (0.03 mg/kg) was administered intravenously. After zoledronic acid, the serum calcium steadily declined and eventually normalized to 10.9 mg/dL on the 10th hospital day, when he was sent home.

Graphs showing the serial changes in serum calcium, urea, and creatinine before and after zoledronic acid administration are shown in Figure 1. His most recent laboratory work-up, 1 year after the described events, shows that his renal function remains stable (serum creatinine 0.68 mg/dL and urea 42.7 mg/dL), while the serum 25(OH)D concentration is 107.9 ng/mL. He remains completely asymptomatic, i.e., with no apparent renal or skeletal consequences.

Figure 1. Serial changes of serum calcium, urea, and creatinine over time. The time-point of zoledronic acid administration is noted (arrow).



3. Discussion

We describe an interesting case of a male toddler with operated posterior urethral valves and a single functioning kidney who developed hypervitaminosis D with hypercalcemia after being instructed to consume orally 6,000 IU of cholecalciferol daily for two months for vitamin D deficiency. To the best of our knowledge, the measured-with an electrochemiluminescence binding assay-concentration of 25(OH)D (3,555 ng/mL) in his blood is the highest we could find in a case of iatrogenic hypervitaminosis D in a child of his age, and the reason we suspected upfront that he had been overdosed with an oral vitamin D supplement. Since the family who was on vacation in Greece followed meticulously the instructions of the treating physician in the United Kingdom, and there was no chance of an accidental overdose, we suspected from the start that the supplement used contained more vitamin D than was written on its label. Indeed, several months after the described events, we were informed by the parents that the vitamin D supplement used was recalled in the United Kingdom (see https://www.rpharms.com/about-us/news/details/Food-Standards-Agency-TriOn-Pharma-recalls-Aactive-D3-2000iuml-supplements-because-of-excess-levels-of-Vitamin-D3).

In our child, the cause of hypercalcemia was not immediately apparent at hospital presentations, i.e., before the laboratory work-up was available. Hypercalcemia in children can be PTH-dependent or PTH-independent, either congenital or acquired [5]. Congenital causes of PTH-independent hypercalcemia, like idiopathic infantile hypercalcemia, Williams' syndrome, and inborn errors of metabolism, were excluded, given our patient's age, normal phenotype, and previous normal serum calcium. Causes of acquired hypercalcemia associated with low-normal PTH are more common in children than PTH-associated hypercalcemia and were considered from the start. These include hypervitaminosis D, endocrinopathies, and granulomatous disorders [5]. The low serum PTH and the extremely high 25(OH)D confirmed hypervitaminosis D as the cause of our child's hypercalcemia.

Vitamin D intoxication, defined as hypercalcemia at serum vitamin D concentrations >375 nmol/L (=150 ng/mL), is rare. Still, it can occur in children who receive inappropriately high doses of vitamin D [6]. Hypercalcemia is proportional to serum 25(OH)D but not 1,25(OH)2D, the levels of which remain normal or slightly elevated [7]. The British Scientific Advisory Committee on Nutrition has accepted the European Food Safety Authority recommendations of a safe upper limit of 1,000 IU/day of supplemental vitamin D for infants up to 1 year old, 2,000 IU/day for children aged 1-10 years old, and 4,000 IU/day for children older than 10 years of age [8]. The Institute of Medicine in the USA states that doses up to 4,000 IU per day are likely safe in pregnant and lactating women [9]. The British guidelines for the management of vitamin D deficiency in primary care recommend using 2,000 IU daily for 6 weeks, followed by maintenance vitamin D supplementation in children with a 25(OH)D concentration < 30 nmol/L [10]. Our patient did not have clinical signs suggestive of rickets. The intoxication was the result of the administration of a product with a higher than intended vitamin D3 concentration, as it was later removed from the British market. Fortunately, no long-term renal or skeletal consequences occurred in our patient, since his renal function appears stable, 1 year after the vitamin D intoxication incident.

The increasing use of vitamin D has provoked a substantial increase in the number of reports of vitamin D intoxication. Many of these cases are the result of inappropriate prescribing, including the use of high-dose over-the-counter preparations or the use of unlicensed products. A 2018 literature search for cases reporting vitamin D intoxication due to overdose identified 13 articles [11]. Patients presented with serum vitamin D concentrations ranging between 150 and 1,220 ng/mL and serum calcium concentrations between 11.1 and 23.1 mg/dL. Most of the reported patients showed symptoms of vitamin D toxicity, while the underlying causes included manufacturing errors, overdosing by patients or prescribers, and a combination of these factors.

Serum calcium levels > 16 mg/dL (4.00 mmol/L) have been described in cases of vitamin D overdose in infants and children [12]. Vitamin D toxicity following medically supervised use of vitamin D has been occasionally reported in adults, too [13-15]. Regarding the therapy of hypercalcemia in our patient, apart from eliminating the calcium from his diet, we treated him aggressively with normal saline. Although we considered using calcitonin, [16,17] it was unavailable to us since it is not commercially available in Greece for some time now. We did not consider denosumab, a RANK ligand inhibitor, because although effective in treating hypercalcemia due to primary hyperparathyroidism [18] and vitamin D intoxication, [19] it is not approved in children, and we have no experience with its use in pediatric patients. In addition, we used glucocorticoids that decrease plasma calcium levels by promoting the synthesis of inactive vitamin D metabolites through the upregulation of the 24-hydroxylase enzyme [6, 20]. None of these therapeutic maneuvers were effective, leading us to use zoledronic acid.

Although zoledronic acid administration requires adequate renal function, and the patient we described had compromised renal function on admission, his renal function had almost normalized by the time zoledronic acid was used. Moreover, the dose chosen (0.03 mg/kg) was low and based on consensus guidelines on the use of bisphosphonate therapy in children and adolescents, [21] and a previous report of successful management of severe hypercalcemia with zoledronic acid [22]. We used zoledronic acid in favor of other antiresorptive agents because we have extensive experience with its use in children with osteoporosis.

4. Conclusion

Vitamin D intoxication can occur due to errors in food fortification, drug formulation, inappropriate prescribing or dispensing, and/or errors in oral administration. In any patient presenting with hypercalcemia, especially in the presence of low-normal PTH, the possibility of vitamin D toxicity should be investigated. Finally, antiresorptive therapy, with low-dose bisphosphonates, is effective in cases of symptomatic hypercalcemia not responding to intravenous hydration, administration of corticosteroids, and elimination of oral calcium intake.

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Research Ethics Committee Approval: We declare that the patient approved the study by signing an informed consent form and the study followed the ethical guidelines established by the Declaration of Helsinki.

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Conflicts of Interest: The authors declare no conflicts of interest.

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