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Case Report

A Case Report of Hypercalcemia from Hypervitaminosis A and D

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Abstract

Introduction: Vitamins and supplements are touted over television and social media to be the cure for anything and everything. A deficiency of vitamin D has been linked to many adverse health outcomes, such as all-cause mortality, cardiovascular disease, decreased bone density, infection, and many others. Vitamin A is responsible for normal cellular immunity, integrity of cells and structural proteins, vital for vision and organogenesis during early fetal development. Both vitamins have become increasingly popular for supplementation by the general population. However, vitamins D and A are both fat-soluble vitamins, with extra intake stored within fat tissue in the body and may lead to toxicity in susceptible patients.

Case Report: The case patient presented with worsening altered mental status and weakness over the past few weeks and was found to have a toxic serum calcium level of 17.4 on admission. He was appropriately treated and returned to baseline. The etiology of his hypercalcemia was determined to be over supplementation with both vitamins A and D.

Discussion: Excessive vitamin D is well known in the literature to cause hypercalcemia. However, the addition of hypervitaminosis A complicated this case due to the complex molecular relationship between the vitamins that is not well understood. The case patient likely took a longer time to return to baseline due to the dual insult of over supplementation with both vitamins.

Conclusion: If a patient presents with hypercalcemia and normal to low parathyroid hormone levels, hypervitaminosis D and/or A should be considered in the differential etiology. Although these reports are rare, the increasing use of vitamins and supplements will likely lead to toxicity in additional patients.

Keywords: Vitamins; Hypercalcemia; Toxicity

Abbreviations

mg: Milligram; L: Liter; mmol: Millimoles; mcg: Microgram; pg: Picogram; nl: Nanoliter; PTH: Parathyroid Hormone; EKG: Electrocardiogram; CT: Computerized Tomography Scan; IU: International Units; kg: Kilogram; IV: Intravenous; SQ: Subcutaneous

Introduction

Vitamins and supplements are touted over television and social media to be the cure for anything and everything. Millions of dollars are spent on this advertising for good reason, it gets patients to "buy into the hype" for curative and emotional benefit. However, these small pills can be harmful if ingested in the wrong manner or at the inappropriate doses.

Vitamin D has become a very popular vitamin product over the last 100 years. It was first used to eradicate rickets in the early 20th century in the United States by fortification of food products like milk [1]. Even with this addition, it is still estimated that over 1 billion persons worldwide are deficient in vitamin D [2]. Since this time, vitamin D deficiency has been linked to many adverse health outcomes, such as all cause mortality, cardiovascular

disease, decreased bone density, infection, and many others [1]. With renewed attention on vitamin D deficits, many patients are now ingesting additional vitamin D, as it is readily available in over-the-counter products and supplements. With increased use of supplements and the fortification of foods with vitamin D, there is a real possibility of overdose with this fat-soluble vitamin as excess intake is stored in adipose tissue, not excreted by the body. There are increasing reports of vitamin D toxicity, with the latest reports from the National Poison Data System showing a mean of 4535 cases per year as of 2011 [3].

Vitamin A is a global name for the fat-soluble family of retinoids which include retinol, retinal and retinyl esters which are combined to form activated or precursor forms of vitamin A. This important vitamin is responsible for normal cellular immunity, integrity of cells and structural proteins, vital for vision and organogenesis during early fetal development [4]. Toxicity of vitamin A results from excessive intake of the preformed vitamin (activated vitamin A) in supplements or from animal products such as eggs, liver, and meat. Vitamin A ingested in plant-based foods like broccoli, carrots, sweet potatoes, and spinach is in the carotenoid form (a vitamin A precursor) which must be hydrolyzed in the small intestine to become active vitamin A [4].

Case Report

The case patient is an 81-year-old male who presented to the emergency room secondary to altered mental status and weakness, worsening over the past 3-4 days. At baseline, the patient is independent with his activities of daily living, walks on a regular basis and gives weekly Bible talks at church. However, over the past week he has become increasingly weaker to the point that his wife had to help him out of his chair. On physical exam, the patient was able to replicate simple motor tasks after multiple attempts. He was also oriented only to his name, not time, place, or situation. His past medical history is significant only for hypertension, skin neoplasm of the nose and blindness in his right eye.

Baseline labs were obtained and revealed a critically high serum calcium of 17.4 mg/dl, high ionized calcium of 2.26 mmol/L, low/normal PTH of 19 pg/nl and a normal albumin of 4.4 g/dl. Patient also had a serum creatinine of 1.89 mg/dl, giving him acute kidney injury (likely from dehydration). EKG, Chest X ray and head CT were all performed and revealed no abnormalities.

Due to the high calcium level and low/normal PTH, overdosage with vitamin supplements were immediately considered. The patient was confused and unable to give any medication history on admission, but his wife stated he has been taking vitamin D drops (10,000 IU) for "years" but has not had any in at least 2 weeks because he is currently out of them at home. She also reports giving him vitamin A 20,000 mcg per day. She doubled his normal vitamin A dose 10 days ago when he had cataract surgery "to aid in recovery of his left eye since he is blind in the right eye".

Patient was immediately given 2 liters of normal saline (NS) as a bolus and started on NS at 250 ml/hr. He also received furosemide 40 mg IV to help excrete calcium in the urine and calcitonin 4 units/kg SQ every 12 hours until his calcium levels began to turn downward. For a more permanent reversal of the calcium levels, zoledronic acid 4 mg IV was given followed by serial calcium levels every 6 hours. Over the next 24 hours, his calcium levels fell steadily, reaching a non-toxic level about 30 hours after presentation to the emergency room.

At this point, the IV fluids and SQ calcitonin were stopped, and serum calcium levels continued to be followed daily.

Labs **Normal Ranges**	**Admission**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
Serum Creatinine (SCr) 0.67-1.10 mg/dl	1.89	1.64/1.53	1.34	1.18	1.01		1.16	1.12	1.12
Calcium 8.6-10.3 mg/dl	17.4	16.1/14.7/13.8/12.6	11.0	10.4	9.9	9.2	8.5	8.5	8.8
Ionized Calcium 1.13-1.32 mmol/L	2.26			1.46	1.38	1.24	1.22		
Phosphorus 2.5-5.0 mg/dl	3.4	2.2	1.7	2.3	3.3	2.0	3.5	1.9	

Vitamin A 22-69.5 mcg/dl		74.4				35.7			
1α,25 di-hydroxy vit D 1,25-$(OH)_2$ Vit D 24.8-81.5 pg/ml		1092.0							
25 hydroxy vit D 25-OH Vit D 30-59.9 ng/ml		>120.0							

Table 1

On day 5 of admission, the patient was back to baseline mental status and was able to corroborate the medication history given by the wife. With this evidence and the corresponding labs, the etiology of his hypercalcemia was confirmed as hypervitaminosis D and A, precipitated by overuse of supplementation.

Discussion

Presentation of this patient with symptoms and critical hypercalcemia independent of parathyroid hormone caused by both vitamin A and D hypervitaminosis was clinically unusual. Reviewing the literature, over 100 case reports of vitamin D medicated hypercalcemia along with reviews of mechanisms and treatment were located within the last 10 years. These cases included both male and female patients from infants to geriatric ages by incorrect or overutilization of supplements, overuse of injectable vitamin D and excessive fortification of milk at a dairy. However, linking vitamin A toxicity and hypercalcemia was a harder task with only one case report located.

Vitamin D_3 (cholecalciferol) is the endogenous form of vitamin D that is formed under the skin due to photolysis from sunlight exposure. Vitamin D_2 (ergocalciferol) is the form of vitamin D found in most supplemental and vitamin products. Both vitamin D_3 and vitamin D_2 are hydrolyzed to 25-hydroxy vitamin D [25-(OH) D]. Rising levels of vitamin D_3 or D_2 cause increased serum levels of 25-(OH) D due to only a partial feedback loop to slow production of this product. The metabolite 25-(OH) D is the major circulating vitamin D product, and its level is measured to determine nutritional vitamin D status, with deficiency currently recognized as a level < 25 ng/ml. When a patient has a state of calcium or phosphorus demand, the 25-(OH) D is hydrolyzed in the kidney to the biologically active 1α,25 di-hydroxy vitamin D [1,25 $(OH)_2$ D]. This activation triggers increased intestinal absorption of calcium by both active and passive transport, causing a rise in serum calcium levels (Figure 1) [5]. Hypercalcemia from vitamin D may be caused by over ingestion of supplements and/or a mutation in the hydrolysis enzyme(s) to activate or inactivate the vitamin D metabolites [5,6].

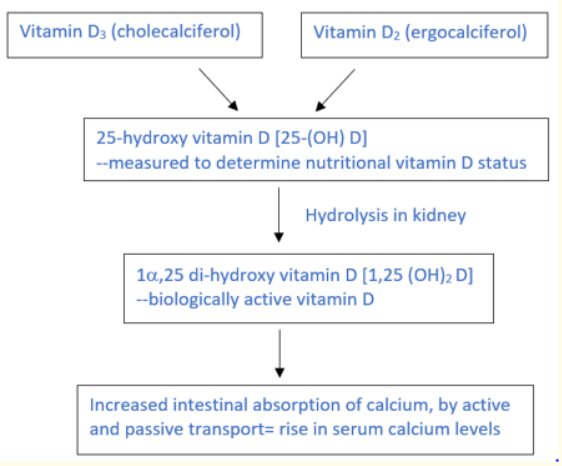

Figure 1: The metabolism of vitamin D [5,6].

The mechanism of vitamin A hypercalcemia is not well understood. Vitamins A and D have a complex molecular transcription level relationship that is poorly understood; however, these vitamins seem to be linked in regulation of gene expression [4,7,8]. The transcription receptors for both vitamins A and D are members of the same family of ligand activated transcription factors. Vitamin D has been shown to activate the retinoid receptors (vitamin A) during transcription and cell proliferation *in vivo* [7]. Thus, both vitamins have similar effects on cells and hormone regulation [7,8]. Current hypotheses for vitamin

A hypercalcemia include increased osteoclast activity, suppression of osteoblasts and hormonal dysregulation of calcium homeostasis due to parathyroid hormone and vitamin D.

The Institute of Medicine and National Institute of Health have defined recommended daily allowances (RDI) for both vitamins A and D in the United States. Vitamin A is measured in retinol activity equivalents (RAE). The RDI of vitamin A is 900 micrograms RAE for men and 700 micrograms RAE for women over the age of 19 [9,10]. The normal reference range for vitamin A is 20-60 mcg/dL, and a toxic level is higher than 65 mcg/dL [4,10]. Vitamin D has a RDI of 600 international units (IU) for adults ages 19-69 and 800 IU for men and women greater than 70 years of age. Vitamin D (25-OH D) levels of 30-59 ng/ml are considered therapeutic and > 60 ng/ml is associated with adverse effects [5,11].

Symptoms of vitamin A and D toxicity overlap and can affect many systems in the body. Commonly seen symptoms include dizziness, vomiting, delirium, confusion, psychosis, dry skin, EKG changes and acute kidney injury complications. Severe hypercalcemia from toxicity of either of these vitamins may occur and persist over long periods of time due to their fat-soluble distribution in the body [1,4]. Therapy for toxicity of either and/or both vitamins include removal of the source of the vitamin A or D from the patient and standard supportive therapies. For vitamin A toxicity, this is the recommended treatment of choice [4].

Treatment of hypervitaminosis D can be divided into several categories. First is stabilization and supportive treatment then correction of hypercalcemia follows. If needed, other therapies can be employed to reduce vitamin D levels [1]. The case patient was started on IV fluids on arrival to the emergency room due to dehydration. Once his calcium level was returned as critically high, the IV fluid rate was increased for volume resuscitation and the patient was monitored closely to maintain his airway and circulation status due to confusion. For immediate lowering of calcium, treatment with loop diuretics and calcitonin is recommended [5]. The case patient received both treatments in the emergency room, and the calcitonin was continued until the calcium down trended. Bisphosphonates, available in IV and oral formulations, are considered the standard of care for hypercalcemia, but usually take 2-4 days to have their full pharmacologic effect [5]. Zoledronic acid IV was given and was the most appropriate choice due to the critical toxicity manifested by this patient. Intermittent hemodialysis may be used in patients with life threatening hypercalcemia or those that become clinically unstable with rising calcium levels [1,5]. Fortunately, the case patient did not require this intervention.

Calcium levels and vitamin D levels were followed appropriately over time to ensure levels were falling and did not increase. More importantly, once the patient was back to baseline mental status, he was able to validate his wife's account of vitamin A and D intake over the last 6 months. His story confirmed the etiology of his hypercalcemia to indeed be excessive ingestion of both vitamins A and D. Although it took about a week for his recovery in the hospital, the patient returned to his normal fully functional status. It is postulated that his recovery was slowed by the dual insult of over supplementation with both vitamins A and D.

Conclusion

Consumption of vitamins A and D above the RDA may indeed cause serious harm to the body. If a patient has hypercalcemia and normal to low parathyroid hormone levels, hypervitaminosis D or A should be considered in the differential etiology. Although these reports are rare, the increasing use of vitamins and supplements will likely lead to toxicity in additional patients.

Conflicts of Interest

The author has no conflicts of interest to declare.

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