

Hipercalcemia e lesão renal aguda causadas por abuso de um composto veterinário parenteral contendo vitaminas A, D e E

Hypercalcemia and acute kidney injury caused by abuse of a parenteral veterinary compound containing vitamins A, D, and E

Authors

Paulo Novis Rocha¹

Caroline Sancho Santos²

Maria Olinda Avila^{3,4,5}

Carolina Lara Neves⁵

Marília Bahiense-Oliveira^{4,5}

¹ Departamento de Medicina da Faculdade de Medicina da Bahia – FMB-UFBA.

² FMB-UFBA.

³ Hospital São Rafael.

⁴ Hospital da Bahia.

⁵ Hospital Ana Nery.

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Correspondence to:

Paulo Novis Rocha
Faculdade de Medicina da Bahia, Universidade Federal da Bahia
Departamento de Medicina e Apoio Diagnóstico
Avenida Reitor Miguel Calmon, s/n – Vale do Canela
Salvador – BA – Brasil
CEP 40110-100
E-mail: paulonrocha@ufba.br

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RESUMO

Um rapaz de 19 anos, previamente hígido, procurou o hospital com queixas de anorexia, náuseas e vômitos. Exames laboratoriais revelaram hipercalcemia (valor máximo do cálcio de 14,8 mg/dL) e lesão renal aguda (valor máximo da creatinina de 2,88 mg/dL). O paciente admitiu utilizar uma formulação parenteral de vitaminas A, D e E de uso exclusivo veterinário, contendo 20.000.000 UI de vitamina A; 5.000.000 UI de vitamina D3 e 6.800 UI de vitamina E, por ampola de 100 mL. Ele refere ter usado cerca de 300 mL do produto no último ano. O jovem não estava interessado na quantidade maciça de vitaminas contida no produto, mas apenas no efeito local do veículo oleoso; o edema provocado pela injeção simulava um aumento de massa muscular. O produto, no entanto, foi absorvido e causou hipervitaminose. O nível sérico de 25(OH) vitamina D estava claramente elevado em 150 ng/mL (referência de 30 a 60 ng/mL), mas não tanto quanto em outros casos publicados de intoxicação por vitamina D. A maioria dos casos de hipercalcemia por hipervitaminose D se associa a níveis de 25(OH)D bem maiores do que 200 ng/mL. O PTH estava indetectável, e outras causas de hipercalcemia foram excluídas. Deste modo, conclui-se que a gravidade da hipercalcemia encontrada neste caso foi resultado do efeito sinérgico da intoxicação pelas vitaminas A e D. O paciente foi tratado com soro fisiológico, furosemida e ácido zolendrônico e evoluiu com normalização rápida dos níveis séricos de cálcio e da função renal.

Palavras-chave: 25-hidroxivitamina D 2. Vitamina A. Overdose. Hipercalcemia. Lesão renal aguda.

ABSTRACT

A previously healthy 19 year-old male presented to the hospital with anorexia, nausea, and vomiting. Laboratory studies were significant for hypercalcemia (peak calcium value of 14.8 mg/dL) and acute kidney injury (peak serum creatinine of 2.88 mg/dL). He admitted to using a parenteral formulation of vitamins A, D and E restricted for veterinary use containing 20,000,000 IU of vitamin A; 5,000,000 IU of vitamin D3; and 6,800 IU of vitamin E per 100 mL vial. The patient stated to have used close to 300 mL of the product over the preceding year. Interestingly, the young man was not interested in the massive amounts of vitamins that the product contained; he was only after the local effects of the oily vehicle. The swelling produced by the injection resulted in a silicone-like effect, which gave the impression of bigger muscles. Nevertheless, the product was absorbed and caused hypervitaminosis. The serum level of 25(OH) vitamin D was clearly elevated at 150 ng/mL (reference range from 30 to 60 ng/mL), but in most published cases of vitamin D toxicity, serum levels have been well above 200 ng/mL. His PTH level was undetectable and other potential causes of hypercalcemia were excluded. Therefore, we posit that the severity of the hypercalcemia observed in this case was the result of a synergistic effect of vitamins A and D. The patient was treated with normal saline, furosemide and zolendronic acid, with rapid normalization of calcium levels and renal function.

Keywords: 25-hydroxyvitamin D 2. Vitamin A. Overdose. Hypercalcemia. Acute kidney injury.

INTRODUCTION

Body builders and professional athletes have for long struggled with the temptation to use performance-enhancing substances. Given modern society's fixation on physical appearance, these substances are being increasingly used by amateurs in gyms around the world. This practice can result in several complications, which can vary according to the type of substance used.

Fitness-related acute kidney injury (AKI) is most often a result of volume depletion or rhabdomyolysis.¹ The use of nonsteroidal anti-inflammatory drugs is another recognized cause of AKI among athletes.² More recently, development of nephrotoxicity has been associated with the use of creatine supplements (interstitial nephritis),³ and anabolic steroids (focal and segmental glomerulosclerosis).⁴ Herein, we report the case of a young man who developed hypercalcemia and AKI due to abuse of a parenteral veterinary compound containing large quantities of vitamins A, D, and E.

MATERIALS AND METHODS

CASE REPORT

A previously healthy 19 year-old male presented to the emergency department complaining of a three-week history of anorexia and nausea. Three days prior to admission, these symptoms worsened and he began to vomit. There was no abdominal pain, diarrhea, fever, jaundice, hematemesis, or melena. The review of systems was noncontributory. He stated occasional alcohol and tobacco use, but denied illicit drug abuse. He admitted to being overly concerned with his body image since a very young age, and to have engaged in several diets. Over the last two years, he had been exercising regularly at a gym, mostly weight lifting.

The patient also admitted to using several over-the-counter food and vitamin supplements but specifically denied abusing anabolic steroids, diuretics, and laxatives. Physical examination revealed normal vital signs and a body mass index of 25 kg²/m². He was awake, alert, and oriented. There was no lymphadenopathy. Pulmonary, cardiac and abdominal exams were normal and he had no peripheral edema. The chest radiograph was normal. Initial laboratory evaluation was remarkable for a serum creatinine of 2.6 mg/dL, total serum calcium of 13.6 mg/dL and ionized calcium of 1.99 mmol/L; urinalysis and renal ultrasound were normal. The 24-hour urine calcium was elevated at 429.7 mg. Uric acid, AST and ALT

levels were slightly increased, but CPK was normal (Table 1).

Notably, an outpatient serum creatinine was 0.7 mg/dL three years ago. A diagnosis of AKI secondary to hypercalcemia was made, and the potential etiologies considered were: vitamin D intoxication; malignancy, such as lymphoma; granulomatous disorders, namely sarcoidosis or tuberculosis; primary hyperparathyroidism; and thiazide diuretic abuse. Given the absence of fever, respiratory symptoms, normal physical exam and normal chest radiograph, we ruled out lymphoma, sarcoidosis, and tuberculosis. The PTH level returned undetectable, ruling out primary hyperparathyroidism. A diagnosis of vitamin D intoxication, suspected on clinical grounds, was confirmed by a toxic 25(OH) D level of 150 ng/mL (reference range from 30 to 60 ng/mL). When confronted with this result, the patient admitted to using a parenteral veterinary compound containing 20,000,000 IU of vitamin A; 5,000,000 IU of vitamin D3; and 6,800 IU of vitamin E, per 100 mL vial (trade name - ADE LABOVET). A friend would typically inject him with approximately 3 mL in each biceps and triceps (total of 12 mL) twice a month; he stated that he might have used close to 300 mL of the product over the preceding year. The product was used for the last time approximately one month prior to admission.

He was initially treated with normal saline at 166 mL/hour. After 24 hours, the spot urinary sodium had increased from 17 to 62 meq/L (data not shown), but there had been no improvement in renal function and total serum calcium remained elevated at 13.6 mg/dL (Table 2). Normal saline infusion rate was increased and intravenous furosemide, added. The patient responded with a brisk diuresis ranging from approximately 5 to 7 L per day, and required magnesium and potassium supplementation. On the fourth hospital day, a 4 mg infusion of zoledronic acid was given. Table 2 shows the evolution of his serum calcium and creatinine levels. The patient was discharged from the hospital on the eighth day with normal serum creatinine and calcium levels. Follow-up data from a clinic visit two weeks after discharge revealed a calcium level of 9.0 mg/dL and creatinine of 0.9 mg/dL (data not shown).

DISCUSSION

This case adds to the nephrology literature regarding the nephrotoxicity of sports-related substance abuse among young individuals. A peculiar aspect of this report was the type of substance abused: a parenteral

Table 1 SUMMARY OF MAIN LABORATORY STUDIES UPON ADMISSION

| Laboratory parameters | Results | Unit | Reference range |
|----------------------------------|---------|-----------------------|-------------------|
| Admission serum urea | 47 | mg/dL | 10 – 50 |
| Admission serum creatinine | 2.64 | mg/dL | 0.9 – 1.3 |
| Total serum calcium | 13.6 | mg/dL | 8.4 – 11.0 |
| Ionized calcium | 1.99 | mmol/L | 1.10 – 1.30 |
| PTH | < 3 | pg/mL | 12.0 – 72.0 |
| Serum alkaline phosphatase | 78 | u/L | 27 – 100 |
| 25 (OH) vitamin D | 150 | ng/mL | 30 – 60 |
| 1,25 (OH) ₂ vitamin D | 26.8 | pg/mL | 18.0 – 78.0 |
| 24-hour urinary calcium | 429.7 | mg/24 h | < 200 mg/24 h |
| Serum pH | 7.38 | NA | 7.35 – 7.45 |
| Serum bicarbonate | 28.7 | mmol/L | 22.0 – 26.0 |
| Spot urinary sodium | 19 | mmol/L | NA |
| Serum phosphorus | 4.52 | mg/dL | 2.50 – 4.50 |
| Serum sodium | 136 | mmol/L | 135 – 148 |
| Serum potassium | 4.4 | mmol/L | 3.6 – 5.0 |
| Serum uric acid | 10.5 | mg/dL | 2.5 – 7.0 |
| Serum CPK | 90 | u/L | 24 – 195 |
| AST | 77 | u/L | 11 – 39 |
| ALT | 47 | u/L | 11 – 41 |
| Serum albumin | 3.6 | g/dL | 3.5 – 5.0 |
| White blood cell count | 13350 | cells/mm ³ | 4000 – 10000 |
| Hemoglobin | 15.2 | g/dL | 13.0 – 16.5 |
| Platelet count | 230,000 | cells/mm ³ | 130,000 – 370,000 |

Note: Conversion factors for units: urea in mg/dL to blood urea nitrogen in mg/dL, ÷ 2.2; vitamin D in ng/mL to nmol/L, x 2.5; NA: not applicable.

Table 2 TREATMENT AND CLINICAL PROGRESS

| | D0 | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 |
|---|------|------|----------|----------|----------|------|----------|------|------|
| 0,9% saline (liters/24 hours) | 2.0 | 3.0 | 4.8 | 7.2 | 7.2 | 7.2 | 4.8 | 4.8 | — |
| Furosemide (mg, route) | — | — | 40 IV | 40 IV | 40 IV | — | 80 PO | — | — |
| Diuresis (liters/24 hours) | NA | 1.7 | 5.3 | NA | 5.1 | 6.9 | 5.2 | 6.4 | 1.4* |
| Zoledronic acid (mg, iv) | — | — | — | — | 4 | — | — | — | — |
| Total serum Ca ⁺⁺ (mg/dL) | 13.6 | 13.6 | NA | 14.8 | 11.9 | 11.0 | NA | 8.8 | NA |
| Ionized serum Ca ⁺⁺ (mmol/L) | NA | 1.99 | 1.93 | 1.86 | NA | 1.69 | NA | 1.28 | 1.16 |
| Serum creatinine (mg/dL) | 2.64 | 2.68 | 2.88 | 2.48 | 2.41 | 1.87 | 1.60 | 1.46 | 1.09 |

D0: day zero (and so on); NA: not available; IV: intravenous; PO: by mouth; *until time of discharge.

veterinary compound containing large quantities of vitamins A, D, and E. Each 100 mL vial of the product contained 20,000,000 IU of vitamin A; 5,000,000 IU of vitamin D3; and 6,800 IU of vitamin E. For every typical 12 mL administration (3 mL in each biceps and triceps), the patient received 2,400,000 IU of vitamin A; 600,000 IU of vitamin D3; and 816 IU of vitamin E. This was done approximately twice a month for a year. This amount is greater than what is recommended for adult bulls (5 mL, every 90 days, according to package insert). The young man was not interested in the massive amounts of vitamins that the product contained; he was only after the local effects of the oily vehicle. The swelling produced by the injection resulted in a silicone-like effect, which gave the impression of bigger muscles. Nevertheless, the product was absorbed and caused hypervitaminosis. The patient said that the choice for this particular product was based on its widespread use among his peers, affordability, and ready availability without prescription in veterinary stores.

Vitamin D toxicity leads to an excessive intestinal calcium absorption, and it is an established cause of hypercalcemia.^{5,6} Acutely, hypercalcemia impairs kidney function by causing direct renal vasoconstriction and by promoting hypovolemia.⁷ The latter may result from the gastrointestinal side effects of hypercalcemia as well as from polyuria, which reflects decreased collecting duct cells response to vasopressin.⁸ These mechanisms of AKI highlight the importance of volume expansion in the early stages of hypercalcemia treatment.

The recommended daily intake of vitamin D varies from 200 (children) to 600 IU (elderly), but much higher doses are necessary for toxicity.⁹ For example, one full-body exposure to sunlight is equivalent to an oral vitamin D intake of 10,000 IU. Since there are no reported cases of vitamin D intoxication from sun exposure, 10,000 IU per day is considered a safe upper level of intake.⁵ Indeed, published cases of vitamin D toxicity with hypercalcemia involve intake of at least 20,000 to 30,000 IU per day.¹⁰ Our patient was injecting approximately 600,000 IU of vitamin D3 twice a month, which is equivalent to 40,000 IU per day. However, his 25(OH)D level was of 150 ng/mL (375 nmol/L), which, although clearly elevated, is lower than what has been observed in previously reported cases of vitamin D toxicity. In the study by Pettifor *et al.*, for example, serum 25(OH)D levels from 11 patients with vitamin D toxicity ranged from 847 to 1,652 nmol/L.¹¹ According to one expert, there are no reported cases of vitamin D

intoxication with serum 25(OH)D levels < 200 ng/mL (500 nmol/L).^{9,10} Therefore, we posit that vitamin A intoxication might have significantly contributed to the hypercalcemia (and ultimately to the AKI) observed in the present report.

Although less common, vitamin A intoxication is also a documented cause of hypercalcemia.¹²⁻¹⁷ The exact mechanism is incompletely understood, but it seems to involve a direct effect on bone, perhaps via up-regulation of osteoclasts by retinol metabolites.¹⁸ The recommended daily intake of vitamin A is 5,000 IU. Patients with renal failure may be particularly prone to vitamin A intoxication, due to decreased metabolism of retinol to retinoic acid and increased concentrations of retinol-binding protein.¹⁸ Farrington *et al.* demonstrated increased vitamin A and calcium levels in a group of hemodialysis patients taking up to 15,000 IU of vitamin A per day. Discontinuation of the supplement resulted in a reduction of vitamin A and calcium levels.¹⁹

Cohen and Trivedi reported a case of hypercalcemia and AKI in a patient that took a 28,000 IU daily dose of vitamin A for macular degeneration; his retinol level was elevated at 2,550 mg/L (reference range from 350 to 1,200 mg/L).¹⁷ Most other reports of hypercalcemia with vitamin A have involved the prolonged use of doses ten times greater than what is recommended. Baxi *et al.* reported a case where a patient took 50,000 IU of vitamin A daily for three months and then raised the dose to 100,000 IU; one week later, he was admitted with symptoms of hypercalcemia and a calcium level of 14.4 mg/dL.¹⁶ Corroborating the hypercalcemic effects of vitamin A, there are several reports of hypercalcemia with all-trans-retinoic acid for the treatment of acute promyelocytic leukemia²⁰⁻²² and with isotretinoin for the treatment of acne.^{23,24} Although we do not have retinol levels, it is estimated that our patient was using close to 2,400,000 IU of vitamin A twice a month, which is 32 times the recommended daily intake, an amount clearly compatible with toxicity. Moreover, since most vitamin A is stored in the liver, circulating serum levels may not be helpful in diagnosing toxicity.²⁵

The use of veterinary ADE by young men is, unfortunately, highly popular in Brazil. A survey conducted among young body builders from a low-income neighborhood in the city of Salvador (Bahia, Brazil) found that the veterinary drug ADE was one of the most common substances used by this population.²⁶ Several references to its use can be found by searching for “*vitamina ADE*” in common Internet search engines, social networks, and video-sharing websites.

However, reports of adverse events of this veterinary vitamin supplement are scarce in the scientific literature. We found only two reports of hypercalcemia and AKI from veterinary ADE abuse.^{27,28} In both reports, however, the patients also used other substances that could have contributed to AKI.^{27,28}

The main objective of this report is to raise awareness of the medical community to the ongoing and dangerous practice of vitamin/supplement abuse by young individuals, which may include drugs reserved for veterinary use. Our case also illustrates how vitamins A and D can act synergistically to cause hypercalcemia. We conclude with the suggestion that overdose with vitamins A and/or D should be considered in the differential diagnosis of hypercalcemia and AKI of obscure etiology.

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