Hypercalcemia and acute renal insufficiency following use of a veterinary supplement

A previously healthy 24 yo male presented with a two-month history of epigastric pain, nausea, vomiting, fatigue and malaise. He reported abuse of different substances, including an injectable veterinary vitamin compound, which contains high doses of vitamin A, D and E, and an oily vehicle that induces local edema and enhances muscle volume. Serum creatinine was 3.1 mg/dL, alanine transaminase 160 mg/dL, aspartate transaminase 11 mg/dL, total testosterone 23 ng/dL, total calcium 13.6 mg/dL, 24-hour urinary calcium 635 mg/24h (RV 42-353). A urinary tract ultrasound demonstrated signs of parenchymal nephropathy. The diagnosis was hypercalcemia and acute renal failure secondary to vitamin D intoxication. He was initially treated with intravenous hydration, furosemide and prednisone. On the fifth day of hospitalization a dose of pamidronate disodium was added. The patient evolved with serum calcium and renal function normalization. Thirty days later he presented normal clinical and laboratory tests, except 25-OH-vitamin D that was persistently increased (107 ng/mL), as it may take several months to normalize. This case report is a warning of the risks related to the use of veterinary substances for aesthetics purposes.

Keywords: hypercalcemia; renal insufficiency; veterinary drugs; vitamin D.

AbstReCT

A previously healthy 24 yo male presented with a two-month history of epigastric pain, nausea, vomiting, fatigue and malaise. He reported abuse of different substances, including an injectable veterinary vitamin compound, which contains high doses of vitamin A, D and E, and an oily vehicle that induces local edema and enhances muscle volume. Serum creatinine was 3.1 mg/dL, alanine transaminase 160 mg/dL, aspartate transaminase 11 mg/dL, total testosterone 23 ng/dL, total calcium 13.6 mg/dL, 24-hour urinary calcium 635 mg/24h (RV 42-353). A urinary tract ultrasound demonstrated signs of parenchymal nephropathy. The diagnosis was hypercalcemia and acute renal failure secondary to vitamin D intoxication. He was initially treated with intravenous hydration, furosemide and prednisone. On the fifth day of hospitalization a dose of pamidronate disodium was added. The patient evolved with serum calcium and renal function normalization. Thirty days later he presented normal clinical and laboratory tests, except 25-OH-vitamin D that was persistently increased (107 ng/mL), as it may take several months to normalize. This case report is a warning of the risks related to the use of veterinary substances for aesthetics purposes.

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ReSUmO

Um paciente de 24 anos do sexo masculino, previamente hígido, apresentou-se com uma história de dois meses de dor epigástrica, náuseas, vômitos, fadiga e mal-estar. Ele relatava abuso de diferentes substâncias, incluindo um composto vitamínico veterinário injetável contendo altas doses de vitamina A, D e E, e um veículo oleoso que induz edema local com aumento de volume muscular. A creatinina sérica estava 3,1 mg/dL, alanina transaminase 160 mg/dL, aspartato transaminase 11 mg/dL, testosterona total 23 ng/dL, 25-OH-vitamina D > 150 ng/mL (toxicidade > 100), 1,25-OH-vitamina D 80 pg/mL, vitamina A 0,7 mg/dL, paratormônio < 3 pg/mL, cálcio total 13,6 mg/dL, cálcio urinário de 24h 635 mg/24h (VR 42-353). Uma ultrassonografia do trato urinário demonstrou sinais de nefropatia parenquimatosa. O diagnóstico foi hipercalemia e insuficiência renal aguda secundária à intoxicação por vitamina D. Ele foi tratado inicialmente com hidratação intravenosa, furosemida e prednisona. No quinto dia de hospitalização uma dose de pamidronato diossódico foi adicionada. O paciente evoluiu com normalização do cálcio sérico e da função renal. Trinta dias depois ele apresentou testes clínicos e laboratoriais normais, exceto a 25-OH-vitamina D que estava persistentemente elevada (107 ng/mL), já que ela pode demorar vários meses para normalizar. Este relato de caso é um alerta aos riscos relacionados ao uso de substâncias veterinárias para fins estéticos.

Palavras-chave: drogas veterinárias; hipercalemia; insuficiência renal; vitamina D.
INTRODUCTION

The society beauty standards change over time, but one characteristic remains: they are generally unreachable for those who did not win the genetic lottery. The widespread idea that a perfect body will bring acceptance and fulfillment lead some individuals to undergo multiple procedures, sometimes harmful, in pursuit of their aesthetic goal.

The consumption of anabolic steroids, supplements and similar products by bodybuilders and athletes grows larger every day. Among many substances, the veterinary supplement ADE - which contains high doses of vitamin A, D and E - has been increasingly used due to its oily vehicle that induces local edema, enhancing muscle volume.\(^1\)\(^3\) Here we report the case of a young man who presented with hypercalcemia and acute kidney injury following ADE injection.

CASE PRESENTATION

A previously healthy 24-year-old male was admitted with a two-month history of progressively worsening epigastric pain, nausea, vomiting, fatigue and malaise. He denied having taken continuous medication, but he reported abuse of different substances aiming muscle mass increase, among these: growth hormone, nandrolone and other testosterone derivatives.

He also reported parenteral application of 150 mL of a veterinary vitamin formulation (ADE) in the previous four months, 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. During the investigation, he had no abnormal findings on physical examination and his body mass index was 25.1 kg/m\(^2\).

Laboratory studies (serum) evidenced: creatinine 3.1 mg/dL (reference value [RV] 0.8-1.3), urea 54 mg/dL (RV 15-39), albumin 3.5 mg/dL (RV 3.4-5.0), alanine transaminase 160 mg/dL (VR 30-65), aspartate transaminase 11 mg/dL (RV 15-37), alkaline phosphatase 87 U/L (RV 50-136), total testosterone 23 ng/dL (RV 72-853), 25-OH-vitamin D > 150 ng/mL (toxicity > 100), 1,25-OH-vitamin D 80 pg/mL (RV 18-78), vitamin A 0.7 mg/dL (RV 0.3-0.7), parathormone < 3 pg/mL (RV 12-65), total calcium 13.6 mg/dL (RV 8.5-10.1) and serology for viral hepatitis and HIV negative. 24-hour urinary calcium was 635 mg/24h (RV 42-353) and urinalysis was normal. Thereafter a urinary tract ultrasound demonstrated signs of parenchymal nephropathy.

The diagnosis was hypercalcemia and acute renal failure secondary to vitamin D (and possibly vitamin A) intoxication. He was treated with vigorous intravenous hydration associated with diuretic (furosemide 80 mg per day) and corticosteroids (prednisone 40 mg per day). On the fifth day of hospitalization a single dose of the osteoclast inhibitor pamidronate disodium 90 mg was added. The patient evolved with serum calcium and renal function normalization, and he was discharged on the 14th day. Thirty days later he was examined at the outpatient clinic, presenting normal clinical and laboratory tests, except 25-OH-vitamin D that was persistently increased (107 ng/mL). Since vitamin D is stored in fat, it may take several months to normalize.

DISCUSSION

Although the vitamin compound ADE is manufactured for strictly veterinary use, it is one of the most commonly used injectable oils by Brazilian bodybuilders, because of its low cost and easy access.\(^6\)\(^7\) This practice is essentially aesthetic and is not considered anabolic because there is no growth of muscle tissue, but muscle swelling.\(^1\)

The recommended dietary allowance for vitamin D in healthy adults is 600 IU,\(^8\) and a much higher intake is required for toxicity. According to most reports, the toxicity threshold is around 10,000 to 40,000 IU a day.\(^9\) This patient has used about 1,875,000 IU/month (62,500 IU/day).

Laboratory tests carried out on admission indicated hypervitaminosis D, which leads to hypercalcemia and related complications, such as secondary hyperparathyroidism and acute kidney injury. High levels of vitamin D result in excessive intestinal calcium absorption, causing acute hypercalcemia, which may impair kidney function by direct vasoconstrictive effects on arteriolar smooth muscle. Furthermore, gastrointestinal side effects of hypercalcemia and polyuria due to nephrogenic diabetes insipidus may result in prerenal involvement.\(^10\)

Although clearly abnormal, the magnitude of the initial 25-OH-vitamin D elevation could not be precisely determined, as the concentration exceeded the upper limit of detection of the assay. Hypercalcemia has also been described as a complication of vitamin A use; therefore it is possible that hypervitaminosis A have contributed to this clinical scenario. The exact mechanism is not completely understood, but some
findings suggest a direct effect of vitamin A on bone.\textsuperscript{11} The tolerable upper intake levels for preformed vitamin A in adults is 10,000 UI.\textsuperscript{12}

Despite presenting a serum retinol level in the upper limit of the reference range, most vitamin A is stored in the liver and the patient had ingested about 7,500,000 UI per month (250,000 UI per day), with a high probability of causing toxicity.\textsuperscript{1}

The use of anabolic steroids has also been associated with nephrotoxicity, although with a different clinical presentation. Focal segmental glomerulosclerosis with marked proteinuria was reported after a bodybuilding regimen consisting of dietary supplements, testosterone and growth hormone.\textsuperscript{13} Despite the absence of specific findings, we cannot rule out the use of these substances as a contributing factor to kidney damage.

Additional alterations observed in laboratory tests were high levels of alanine transaminase and low levels of total testosterone. Liver injury has been consistently reported due to anabolic steroids abuse, and may include hepatotoxicity, non-alcoholic fatty liver disease and liver neoplasm.\textsuperscript{14} Hypervitaminosis A can also produce liver damage, presenting as alterations in liver profile, cholestasis, non-cirrhotic portal hypertension, chronic hepatitis and cirrhosis. Toxicity of vitamin A is apparently a dose-dependent effect of retinoids on hepatic stellate cells.\textsuperscript{14}

Regarding testosterone, hypogonadism is a common side effect of anabolic-androgenic steroids, as a result of feedback suppression of the hypothalamic-pituitary-gonadal axis. The duration of suppression and the resultant low testosterone levels are highly variable and depend on multiple factors, including type of drug, dose and length of exposure.\textsuperscript{13}

Fortunately, the patient had reversal of the situation without serious sequelae. The main objective of this report is to warn the medical community and overall population of the risks related to the use of veterinary substances for aesthetics purposes. A few similar cases have been reported, mostly from Brazil.\textsuperscript{13} Reports regarding this practice are scarce on scientific literature, although extensively covered in the lay press and bodybuilding websites.

**References**