



Hepatotoxicity Associated with Nutritional Supplements Containing Anabolic Steroids

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Abstract

Background and Objectives: The objective of this article was to emphasize the hepatotoxicity associated with the use of nutritional supplements and anabolic-androgenic steroids, as well as discussing the sale of the latter as a dietary supplement.

Methods: This is a case series of two patients who developed hepatic damage after the consumption of anabolic-androgenic steroids, accompanied by a detailed bibliographic research on this topic.

Results: We present two young men who developed significant liver damage, both with hyperbilirubinemia pattern after consumption of anabolic-androgenic steroids. This was associated with considerable morbidity, although both recovered without liver transplantation. The two anabolic-androgenic steroids were being marketed as dietary supplements.

Conclusions: Although classified as Class V controlled substances in Brazil, anabolic-androgenic steroids are the cause of severe hepatotoxicity. Although the National Sanitary Surveillance Agency acts in the regulation of such substances, some of these products are still marketed as dietary supplements, requiring a more rigorous surveillance by health professionals.

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Introduction

Testosterone was discovered and isolated in 1935 and since then there have been several attempts to develop synthetic derivatives (usually by 17 α -alkylation) with the goal of making it orally active and prolonging its biological activity [1,2]. Many of these products, commonly known as Anabolic-Androgenic Steroids (AAS), have been developed, being more anabolic and less androgenic than their parent molecule [2]. The most commonly used derivatives include nandrolone, oxandrolone, stanozolol and oxymethylene. There are some clinical situations that suggest their use, especially for conditions such as cachexia [3] related to the immunodeficiency virus and aplastic anemia [4]. However, they came to discredit after the use by athletes in order to boost performance. In 1975, the International Olympic Committee Medical Committee added anabolic steroids to its list of banned substances, and in 1991 all these were classified as class III controlled substances (Anabolic Steroids Control Act of 1990). Pub. L. 101-647.1901, 104 Stat. 4851) by the Food and Drug Administration. In spite of this, many anabolic steroids are available in natural products stores and can also be purchased easily on the internet. What is more worrying is that they are being marketed as dietary supplements. To increase awareness of this problem and to highlight hepatic side effects, we report two clinical cases of young men developing potentially fatal hepatotoxicity after consumption of M-STANE (2 α ,17 α -dimethyl-5 α -androst-3-one-17 β -ol 10 mg) which contains ultradrol, aprehormone that, once consumed, is metabolized as a steroid, and WINSTROL (stanozolol), considered a pure anabolic-androgenic steroid.

Case Presentation

Case 1

A 21-year-old male construction worker was referred to Antônio Pedro University Hospital in January 2014 with a history of diffuse abdominal pain, jaundice, choluria, acholic feces and severe pruritus, as well as an 18-kilogram weight loss in the last three months. There was no history of altered mental status. There was a report of illicit drug use from age 14 to 16, and former smoker 10 packs • year (quit five years ago); without associated diseases. He admitted to using M-STANE one month prior to the start of his clinical condition, 2 capsules / day (dose recommended by the manufacturer) for a total of four weeks from October to November 2013. M-STANE was obtained from a “natural products” store, according to the patient’s report. The patient denied any prior

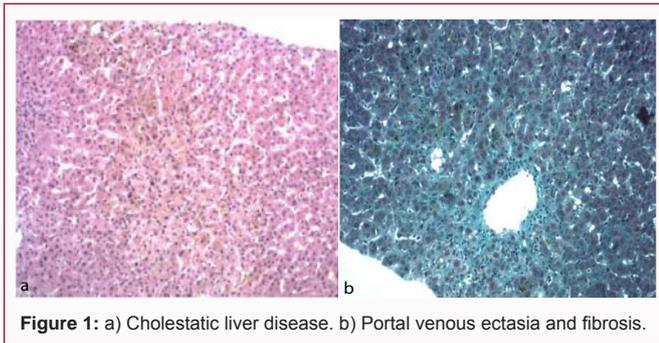


Figure 1: a) Cholestatic liver disease. b) Portal venous ectasia and fibrosis.

liver disease, excessive alcohol intake, medication use or travel; as well as family history of liver disease. At admission the patient was hemodynamically stable, but had a marked conjunctival jaundice. His liver was palpable 2 cm below the right costal border. However, there was no evidence of fluid overload or hepatic encephalopathy. Initial laboratory results revealed a total bilirubin level of 27.2 mg/dL (0.1-1.2 mg/dL), the conjugated fraction was 21.2 mg/dL; alanine aminotransferase 38 U/L (16-63 U/L); aspartate aminotransferase of 54 U/L (15-37 U/L); 701 U/L alkaline phosphatase (46-116 U/L); a gamma-glutamyltransferase of 61U/L (15-85 U/L); serum albumin of 2.8g/dL (3.5-5.3 g/dL); INR of 1.1. Viral serologies for hepatitis A, B and C, Epstein-Barr virus, cytomegalovirus as well as anti-nuclear antibody titers, antimitochondrial antibody, and anti-smooth muscle antibody were all negative. Ultrasonography showed no evidence of biliary obstruction or chronic liver disease. Hepatic biopsy was performed, whose histopathological study revealed cholestatic liver disease with marked cholestasis and porto-portal fibrosis, in addition to the presence of portal venous ectasia (Figures 1A and 1B). We chose a conservative treatment with ursodeoxycholic acid 900 mg/day. The patient had jaundice (4+/4+) when he was discharged, without signs of encephalopathy, with a prothrombin time of 100% and in a good physical status. Figures 2A and 2B show the course of hyperbilirubinemia as well as an isolated peak of alkaline phosphatase reaching a level of 701 U/L in the absence of a change in the level of gamma-glutamyltransferase. Jaundice resolved over a period of 8 weeks. At this time ursacol was suspended because the patient had no pruritus. At the last follow-up evaluation in August 2015, the total bilirubin level was 0.34 mg/dL with alkaline phosphatase of 122U/L.

Case 2

The second patient was a 28-year-old man, a bricklayer, who was referred to the hepatology department of Antônio Pedro University Hospital in January 2017 for diagnostic elucidation. He presented as symptoms: progressive jaundice, choloria, acholic feces and also reported a weight loss of 10 kilograms in the last three months and pruritus. He reported using Winstrol (stanozolol) for three weeks, in October 2016. He obtained the product from a professional at the gym. The patient denied any prior liver disease and had a history of eventual smoking and social drinking, although he denied any significant ingestion in the four weeks preceding the condition. On physical examination, he had a significant conjunctival jaundice and hepatomegaly of +/- 18cm. He was alert and oriented. The hepatic profile showed: total bilirubin level of 18.8 mg/dL, with the conjugated fraction being 11.94 mg/dL; albumin of 4.26 g/dL; alkaline phosphatase of 200U/L; 42U/L gamma-glutamyltransferase; 38U/L aspartate aminotransferase; 156U/L alanine aminotransferase; international standard rate for prothrombin time was normal and viral serologies and autoantibodies were negative. Ultrasonographic

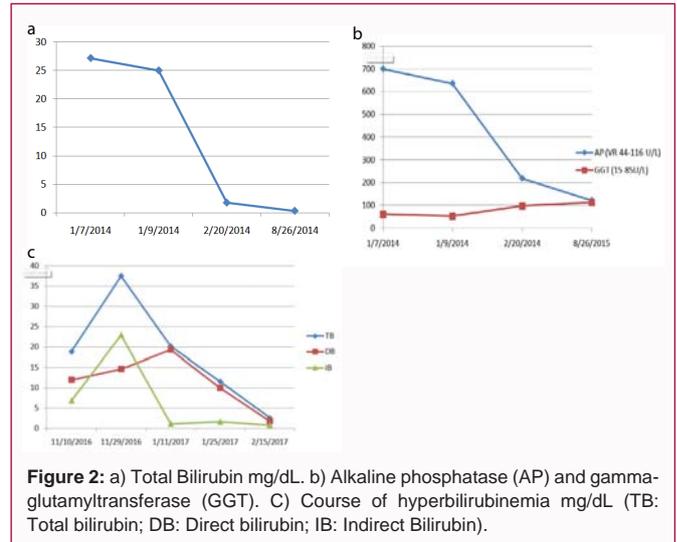


Figure 2: a) Total Bilirubin mg/dL. b) Alkaline phosphatase (AP) and gamma-glutamyltransferase (GGT). c) Course of hyperbilirubinemia mg/dL (TB: Total bilirubin; DB: Direct bilirubin; IB: Indirect Bilirubin).

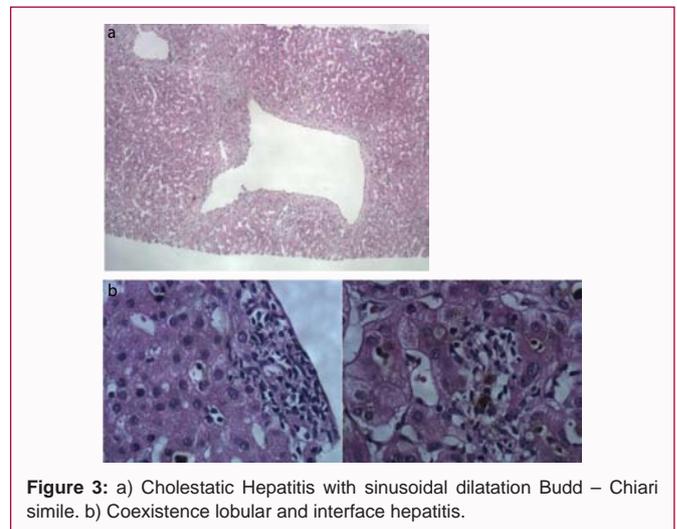


Figure 3: a) Cholestatic Hepatitis with sinusoidal dilatation Budd – Chiari simile. b) Coexistence lobular and interface hepatitis.

imaging showed a regular and homogeneous enlarged liver (reaching the right flank), with no evidence of intra- or extra-hepatic dilatation. The patient was treated conservatively with symptomatic treatment, as an outpatient. However, there was no significant improvement in bilirubin levels even with the AAS suspension since the onset of the clinical condition. A hepatic biopsy with subsequent histopathological study (Figure 3A and 3B) revealed cholestatic hepatitis with sinusoidal dilatation (SOS/VOD) Budd-Chiari simile, compatible with anabolic use, in addition to coexisting lobular and interface hepatitis suggestive of autoimmune hepatitis, possibly induced by the substance. Presence of portal fibrosis with short fibrous septa (F2). He was discharged with cholestyramine, hydroxyzine, ursodeoxycholic acid; the use of latter two being suspended by the patient himself two weeks later, due to diarrhea. The total bilirubin level reached a peak of 37.5 mg/dL (Figure 2C). Later on, hyperbilirubinemia showed a gradual decrease. At the last clinic appointment in February 2017, total serum bilirubin levels were 2.55 mg/dL and transaminases were within normal limits.

Discussion

The two patients mentioned presented an important hepatic injury due to the use of AAS. Our first patient was consuming M-STANE, which contains a pre-hormone called ultradrol that stimulates the conversion of synthetic substances from the supplement, leading

to a high hormonal load. This has the same function as pure AAS. Our second patient used Winstrol. It contains a synthetic steroid derived from testosterone called Stanozolol, which has the purpose of decreasing the glycoprotein SHBG, responsible for the binding of some hormones, such as testosterone. The decrease in SHBG causes free testosterone to increase, favoring its effects. Because of the serological and epidemiological exclusion of other causes and the compatibility in liver histopathology, the AAS consumed by these two patients was the most likely cause of hepatotoxicity. Initially, other causes of liver disease were excluded and imaging studies revealed no evidence of biliary obstruction. The second patient had a history of alcohol consumption, but the biopsy was not compatible with an alcohol-induced injury. It should be emphasized that pre-existing liver disease or the concomitant use of other drugs may increase the hepatotoxicity associated with AAS [2]. Thus, it is conceivable that alcohol may have increased susceptibility to hepatic injury induced by AAS in our second patient. Furthermore, hepatic biopsy in both patients was consistent with AAS-induced hepatotoxicity [5-8]. Finally, both LFT results showed spontaneous improvement after discontinuation of the substance.

Currently, AASs are classified as controlled substances (The Anabolic Steroid Control Act of 1990 [section 21 U.S.C. 844]), therefore, the mere possession, manufacture and distribution of these products (except for strict medical prescription) is considered illegal. However, in spite of this, AAS are not only available on the internet and in "natural products" stores, but are also being marketed as dietary supplements [6,9-11] Shipley's Washington Post article drew attention to the following six anabolic steroids sold as supplements: halodrol-50, Ergomax LMG (Anabolic Resources LLC) (contain madol); Superdrol (Anabolic Resources LLC), Prostanazol (Anabolic Resources LLC) (similar to stanozolol), FiniGenX Magnum Liquid (PharmGen X, San Marcos, CA) (similar to nandrolone); and Methyl 1-P (Legal Equipment-LG Sciences, Brighton, MI) (contains two steroids, progestin, and a second steroid that resembles androstenedione).

In addition to that, the classification of AAS as controlled substances did not prevent its increasing use. Anabolic steroid use among high school seniors increased from about 2% in the early 1990s to 3.4% in 2004 in the United States [12]. Men are more likely to use AAS compared to women, [4] and recent data indicate that currently about 1 million men consume AAS in the United States [12]. Four out of five AAS users take the drug for cosmetic reasons only [13]. Most AAS consumers seek immediate aesthetic results, and therefore do not mind their possible side effects. The psychiatric community identified some of these individuals as having muscle dysmorphia, a condition also known as reverse anorexia nervosa [14]. In an internet search on AAS we found an anonymous questionnaire on a popular website among users of these products. Of the 500 AAS users who answered the questionnaire, 78% were not bodybuilders; about 60% reported using at least 1000 mg of testosterone or its equivalent per week (self-administered at 99%), 13% were using unsafe injection practices, and almost all reported subjective side effects after the use of AAS [13]. Several side effects that have been reported with the use of AAS include unfavorable lipid profile and atherogenesis [15], suppressed endogenous testicular function, growth retardation, neuropsychiatric effects, nephrotoxicity (including rare Wilms' tumors), [12,16,17] and, finally, hepatic side effects. Hepatic changes include peliosis hepatis (cystic blood-filled cavities in the liver), hepatic adenomas, hepatocellular carcinomas, and hepatotoxicity [16,18,19].

In a study in patients with aplastic anemia who received AAS, 35.5% had altered liver function test results, although only half of them (17.3%) developed jaundice [20]. In most cases, cholestasis improved with supportive therapy after 12 months of AAS discontinuation [21,22]. Pruritus responded to choleretic agents such as ursodeoxycholic acid [23,24]. Although, in most cases, cholestasis has been described as benign, fatal cases, although rare, have been reported [22]. Cholestasis induced by AAS is pure (i.e., not associated with hepatocellular damage). Rarely, however, a lesion similar to hepatitis may occur [25]. Cholestasis results from a change in hepatocyte biliary secretion [26]. Mechanisms, however, remain speculative. Studies in rats (Welder et al. [27]) showed that hepatotoxicity and increased levels of liver enzymes were drug-specific changes and that AAS had direct toxic effects on hepatocytes. Other animal studies indicated that oxidative stress could play a role [28], which in turn may result in impairment of the canalicular bile salt export pump [29]. Structural changes induced by AAS include degenerative effects on mitochondria and lysosomes [30].

In conclusion, although AAS-induced cholestasis is uncommon, it is potentially fatal and is associated with significant morbidity. This is well prominent in the cases presented in this report. Besides that, health professionals need to maintain a high level of vigilance over this scenario. It is important to regularly inquire patients about the consumption of AAS or dietary supplements. Also, it is imperative to educate our patients about the hepatotoxicity associated with the use of this class of products.

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