Case Report

ACUTE HEPATITIS AND FEVERS IN AN AMATEUR BODY-BUILDER: A NEW COMPLICATION OF SYNTHETIC ANDROGEN ABUSE?

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ABSTRACT

Objective: Although the illicit use of synthetic androgens is common among amateur body builders in Australia, the toxicology of these drugs is largely limited to case reports, and the health effects are not well understood. Furthermore, combined use with off-label prescription drugs carries undefined medical risks.

Methods: We describe a 35-year-old male amateur body-builder who developed acute hepatitis with accompanying fever.

Results: This phenomenon occurred several weeks after he commenced high-dose methandrostenolone, a nonmarketed 17-alpha-alkylated synthetic androgen available over the internet or in gyms, in combination with anti-estrogen drugs to purportedly prevent gynecomastia and diuretics to lower body weight prior to a body-building competition.

Conclusion: In the absence of infection, this is the first reported case of acute hepatitis occurring in association with fever secondary to the use of a 17-alpha-alkylated androgen. This case serves to increase public, physician, and health authority awareness of this prevalent form of drug abuse and toxicity. **(Endocr Pract. 2014;20:e130-e133)**

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CASE REPORT

We report the case of a 35-year-old male body-builder who presented with a 7-day history of fevers, generalized myalgia, and abdominal pain. Six weeks prior to presentation, he had commenced a rigorous exercise program and an intensive course of both a synthetic androgen and testosterone in preparation for an amateur body-building competition. He purchased methandrostenolone, a synthetic androgen, via a Thai-based website and took this at a reported dose of 100 mg daily for 6 weeks (Fig. 1). The patient had a history of synthetic androgen abuse over the last 10 years, self-administered in cycles of 6 to 10 weeks, with a 2- to 3-week suspension period between cycles. In addition, over a period of 2 weeks prior to admission he took tamoxifen (20 mg daily) and letrozole (2.5 mg daily), purportedly to prevent gynecomastia, as well as frusemide (80 mg daily) and spirinolactone (50 mg daily) to lower body weight prior to competition. In addition, he also self-administered 2 intramuscular injections of testosterone enanthate and propionate in the week prior to presentation (veterinary products, source and dose unspecified).

At presentation he had a body weight of 120 kg (265 lb) with well-developed musculature (Fig. 2), small bilateral testes (volume 6 mL), and male-pattern baldness. Initial examination demonstrated fevers as high as 39°C, sinus tachycardia, blood pressure of 130/90 mm Hg and dehydration. He had right-sided abdominal tenderness, hepatomegaly, and scleral icterus. There was no clinical source of infection and no deep muscle abscesses around the sites of his previous intramuscular injections. He denied a history of alcohol abuse.

A diagnosis of acute hepatitis was made based on markedly elevated liver enzymes (bilirubin 3 mg/dL [<1.2], aspartate aminotransferase [AST] 1,386 U/L [<45], alanine aminotransferase [ALT] 1,231 U/L [<47], g-glutaminyl-transpeptidase [GGT] 133 U/L [<43], alkaline phosphatase [ALP] 116 U/L [30-115]) and impairment of liver synthetic function (protein 5.2 dg/L [6.3-8.9], prothrombin time 19s [10-16]), which was consistent with hepatic necrosis. An

abdominal ultrasound demonstrated an enlarged liver with a span of 22 cm, and testing for viral (hepatitis A, B, C; cytomegalovirus; Epstein-Barr virus) and autoimmune (autoimmune hepatitis, primary biliary sclerosis, primary sclerosing cholangitis) hepatitis was negative. There was no evidence of systemic infection on the basis of multiple urine and blood cultures. In the absence of rhabdomyolysis (creatine kinase [CK] 94 U/L [55-170]), acute renal failure was considered secondary to the use of diuretics and subsequent dehydration (urea 55 mg/dL [9-19.9], creatinine 1.5 mg/dL [0.62-1.2]). Transthoracic echocardiography demonstrated cardiac hypertrophy, which was attributed to chronic androgen abuse.

Hormonal analysis demonstrated complete suppression of blood gonadotropins (undetectable serum luteinizing hormone [LH] and follicle-stimulating hormone [FSH], <1 IU/mL) with a total testosterone of 484 ng/dL (sex hormone-binding globulin [SHBG] 1.46 μg/ml [1.12-5.62]) consistent with the use of exogenous testosterone, possibly with a concomitant synthetic androgen.

Following supportive therapy comprised of intravenous fluid therapy, cessation of his self-prescribed drug cocktail, and close monitoring in a high-dependency unit, his condition gradually improved over 48 hours. His fevers resolved in the absence of antibiotic therapy, and his renal dysfunction normalized with gradual rehydration. After an additional 5-day period of convalescence, his liver function tests had markedly improved (Table 1), and he declined a liver biopsy. He was subsequently discharged with resolution of previous symptoms, but attempts to re-establish contact to repeat liver function tests were unsuccessful as he declined follow-up.

In the absence of evidence of systemic infection, including absence of leukocytosis (maximal white cell count 6.1×10^9/L [3.7-9.5]), the patient's fevers were considered to represent a heightened inflammatory response to the acute hepatitis (C-reactive protein [CRP] 172 mg/L [<10]). Although the patient was on multiple agents and a clear causal relationship could not be ascertained, the 17-alkylated synthetic androgen, methandrostenolone, was the most likely cause of his hepatitis due the sustained high-dose use of this known hepatotoxic agent (1-3).

DISCUSSION

The use of synthetic androgens, sometimes referred to by the misnomer "anabolic-androgenic steroids" (4), is reportedly widespread but illicit, making the prevalence rates of use and adverse effects in the community difficult to measure and likely underestimated. The patterns of illicit androgen abuse typically include high doses and multiple androgens together with many additional drugs intended to prevent or combat side-effects and/or enhance androgen effects (5). Although a survey of Australian high-school

Fig. 1. Photo showing the subject's sample of Dianobol (methandrostenolone) purchased over the internet from a Thai-based website.

Fig. 2. Photo showing the subject in a body-building pose several months prior to presentation

Table 1
Patient's Liver Function Test Results

	Day 1	Day 3	Day 5	Day 7[a]
Urea [9.0-19.9 mg/dL][b]	55.7	44.8	29.1	26.6
Creatinine [0.62-1.19 mg/dL]	1.54	1.6	1.1	1.17
Bilirubin [<1.2 mg/dL]	3.04	3.1	2.9	1.64
ALT [<47 U/L]	1,231	1,129	906	619
AST [<45 U/L]	1,386	1,264	1,022	440
GGT [<43 U/L]	133	127	149	226
ALP [30-115 U/L]	116	108	114	112
Protein [6.3-8.4 g/dL]	5.2	5.3	4.9	5.6
Prothrombin time [10-16 s]	19	17	16	15

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; GGT = γ-glutaminyltranspeptidase
[a] On the day of discharge, test values had not entirely normalized but it was not possible to further monitor these values as the patient declined follow-up.
[b] Normal ranges are shown in brackets

students in the 1990s found that 3% of adolescent males admitted ever taking synthetic androgens (6), there is little known about the prevalence of androgen abuse among young adults in the community or in elite sports. Various adverse effects have been reported, including dyslipidemia, fatal myocardial infarction, neuropsychiatric effects, and hepatic injury (7-10).

The spectrum of hepatic injury resulting from the use of synthetic androgens is wide but remains poorly understood, as the majority of clinical experience derives from case reports (1). Jaundice with intrahepatic cholestasis and hepatocellular necrosis on biopsy are the most frequently described abnormalities (1,10,11). In our subject, marked elevation of transaminases and impaired liver synthetic function were consistent with hepatocellular necrosis. Recovery typically occurs within weeks after drug cessation, and jaundice does not necessarily recur with resumption of synthetic androgen use (3). Death is a highly unlikely consequence and has previously been reported only in elderly or very ill patients who received synthetic androgens for various medical indications prior to their being superseded by other drugs or removal from the pharmaceutical market (12). However, impurities in illicit products may result in death, as recently reported in a male with arsenic toxicity who was taking multiple performance-enhancing substances (13).

The occurrence of fever in association with hepatitis due to synthetic androgen use has not previously been reported. It is possible that the release of hepatic inflammatory proteins (e.g., interleukin [IL]-6 and CRP) was responsible for the fever. Alternatively, the synthetic androgen may have directly altered hypothalamic thermostat function. This is possible as synthetic androgens are known to have effects on central neurotransmitters (14).

Rarer effects include the development of hepatic tumors, particularly hepatocellular carcinoma and peliosis hepatitis, a life-threatening condition characterized by blood-filled cysts in the liver (3,15). Injury is related to the dosing (16) and type of the synthetic androgen use with 17-alkylated androgens (methyltestosterone, methandrostenolone, oxandrolone, and stanazol) being responsible for liver damage (1,2,10,11,16). In addition, the accessory use of other potentially hepatotoxic agents in such risk-taking individuals, such as tamoxifen in our subject, may compound the injury and complicate the identification of the chief offending agent.

Methandrostenolone (also known as methandienone or Dianabol) is an orally active androgen due to its 17-alpha alkylation. This substituent facilitates both oral bioavailability and hepatotoxicity because of its resistance to first-pass hepatic metabolism, a feature which otherwise renders all orally consumed nonalkylated androgens inactive. Once marketed (in the 1960s), it is no longer approved by drug regulatory authorities, and possession is illegal in most countries. Nevertheless it is a popularly abused synthetic androgen; it is the 2nd most popular synthetic androgen (after stanozolol) used in sports doping (17). It is mostly available illicitly via the internet where there is no control on drug purity, contaminants, forgeries, or dosage (18).

CONCLUSION

Although cases of severe hepatitis have been reported in patients taking methandrostenolone, this is the first report of a patient with sufficiently severe hepatitis to induce a systemic inflammatory reaction that primarily manifested as high-grade fevers. The severity of the hepatic necrosis may have been itself related to fever development. This draws attention to the potentially toxic effects of synthetic androgens alone or in combination with multiple drugs as part of the risk-taking behavior amongst some body builders. More systematic research is required into other potentially underrecognized side effects of synthetic androgens to increase public, physician, and health authority awareness of this form of drug abuse and toxicity.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Ishak KG, Zimmerman HJ.** Hepatotoxic effects of the anabolic/androgenic steroids. *Semin Liver Dis*. 1987;7:230-236.
2. **Hild SA, Attardi BJ, Koduri S, Till BA, Reel JR.** Effects of synthetic androgens on liver function using the rabbit as a model. *J Androl*. 2010;31:472-481.
3. **Friedl K.** Reappraisal of the health risks associated with the use of high doses of oral and injectable androgenic steroids. In: Lin EL, ed. *Anabolic Steroid Abuse*. Collingdale, PA: Diane Publishing; 1996.
4. **Handelsman DJ.** Commentary: androgens and "anabolic steroids": the one-headed janus. *Endocrinology*. 2011;152: 1752-1754.
5. **Parkinson AB, Evans NA.** Anabolic androgenic steroids: a survey of 500 users. *Med Sci Sports Exerc*. 2006;38: 644-651.
6. **Handelsman DJ, Gupta L.** Prevalence and risk factors for anabolic-androgenic steroid abuse in Australian high school students. *Int J Androl*. 1997;20:159-164.
7. **Vanberg P, Atar D.** Androgenic anabolic steroid abuse and the cardiovascular system. *Handb Exp Pharmacol*. 2010; 411-557.
8. **Kennedy MC, Lawrence C.** Anabolic steroid abuse and cardiac death. *Med J Aust*. 1993;158:346-348.
9. **Pope HG Jr, Kouri EM, Hudson JI.** Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. *Arch Gen Psychiatry*. 2000;57:133-140; discussion 155-156.
10. **Sánchez-Osorio M, Duarte-Rojo A, Martínez-Benítez B, Torre A, Uribe M.** Anabolic-androgenic steroids and liver injury. *Liver Int*. 2008;28:278-282.
11. **Evans NA.** Current concepts in anabolic-androgenic steroids. *Am J Sports Med*. 2004;32:534-542.
12. **Wilder EM.** Death due to liver failure following the use of methandrostenolone. *Can Med Assoc J*. 1962;87:768-769.
13. **Perera NJ, Steinbeck KS, Shackel N.** The adverse health consequences of the use of multiple performance-enhancing substances--a deadly cocktail. *J Clin Endocrinol Metab*. 2013;98:4613-4618.
14. **Oberlander JG, Porter DM, Onakomaiya MM, et al.** Estrous cycle variations in GABA(A) receptor phosphorylation enable rapid modulation by anabolic androgenic steroids in the medial preoptic area. *Neuroscience* 2012; 226:397-410.
15. **Velazquez I, Alter BP.** Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol*. 2004;77:257-267.
16. **Stimac D, Milić S, Dintinjana RD, Kovac D, Ristić S.** Androgenic/Anabolic steroid-induced toxic hepatitis. *J Clin Gastroenterol*. 2002;35:350-352.
17. WWA-D. http://www.wada-ama.org Laboratory statistics.
18. **van der Kuy PH, Stegeman A, Looij BJ Jr, Hooymans PM.** Falsification of Thai dianabol. *Pharm World Sci*. 1997; 19:208-209.