JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, 2014
doi: 10.1111/1556-4029.12424
Available online at: onlinelibrary.wiley.com

PAPER

TOXICOLOGY; PATHOLOGY/BIOLOGY

Shane Darke,[1] *Ph.D.; Michelle Torok,*[1] *M.Soc.Sci.; and Johan Duflou,*[1,2,3,4] *M.Med.Path. (Forens), F.R.C.P.A.*

Sudden or Unnatural Deaths Involving Anabolic-androgenic Steroids*

ABSTRACT: Anabolic-androgenic steroids (AASs) are frequently misused. To determine causes of death, characteristics, toxicology, and pathology of AAS positive cases, all cases (n = 24) presenting to the New South Wales Department of Forensic Medicine (1995–2012) were retrieved. All were male, and the mean age was 31.7 years. Deaths were mainly due to accidental drug toxicity (62.5%), then suicide (16.7%) and homicide (12.5%). Abnormal testosterone/epitestosterone ratios were reported in 62.5%, followed by metabolites of nandrolone (58.3%), stanozolol (33.3%), and methandienone (20.8%). In 23 of 24 cases, substances other than steroids were detected, most commonly psychostimulants (66.7%). In nearly half, testicular atrophy was noted, as was testicular fibrosis and arrested spermatogenesis. Left ventricular hypertrophy was noted in 30.4%, and moderate to severe narrowing of the coronary arteries in 26.1%. To summarize, the typical case was a male polydrug user aged in their thirties, with death due to drug toxicity. Extensive cardiovascular disease was particularly notable.

KEYWORDS: forensic science, steroids, toxicology, psychostimulants, cardiovascular disease, demographics

Anabolic-androgenic steroids (AAS) include exogenous testosterone, synthetic testosterone, and synthetic testosterone derivatives (1). While such drugs have valid medical applications, human and animal AAS are frequently misused to enhance athletic performance, strength, and image (e.g., body building) (2–7). Users of these drugs are mostly male, and aged predominantly between the late teens and mid-thirties (2–8). Apart from muscular development, the regular use of AAS is associated with a number of direct physiological changes, including testicular atrophy and arrested spermatogenesis, while females may experience masculinization (1). There is also evidence of a dependence syndrome among regular users (9,10). Indeed, in one recent study of AAS users, 30% met DSM criteria for dependence (10).

There is emerging evidence that the use of AAS is associated with increased risk of premature mortality (7,11,12). Much of this risk is thought to arise from the physiological and psychological sequelae of AAS. There is mounting evidence that these drugs cause cardiovascular disease, including cardiomegaly, left ventricular hypertrophy, cardiomyopathy, ischemic heart disease, fibrosis, and contraction band necrosis (1,12–19). Indeed, it has been noted that the profile of cardiovascular damage from AAS abuse is similar to the pathology seen from psychostimulant abuse (1,7,18). Liver disease also appears higher among AAS users, with increased risk of peliosis hepatitis, cholestasis, and hepatic tumors (1,7,18). AAS are also psychotropic and are associated with increased aggressiveness, agitation, paranoid ideation, mood swings, and depression (1,11,12). In the few steroid positive case series that have been conducted, death by violence, from other or to self, formed a substantial proportion of deaths (11,12).

One final factor that may contribute to premature mortality among AAS users is polypharmacy. There is emerging evidence, among both current users and fatalities, that substance use among this population extends far beyond AAS (3,5,20–22). There appear to be increased rates of use of opioids and psychostimulants in particular but, apparently, not of cannabis or tobacco.

Despite their widespread use, there are few case series of steroid positive cases of unnatural or sudden death. This study aimed to determine the circumstances of death, demographic characteristics, toxicology, and major organ pathology of cases presenting to the Department of Forensic Medicine (DOFM), Sydney, over the period January 1, 1996 to December 31, 2012 in which anabolic steroids were detected during quantitative toxicological investigations.

Methods

Case Identification

All cases autopsied at the DOFM between January 1, 1996 and December 31, 2012 were identified in which anabolic steroids were detected in urine taken at autopsy. Police death investigation summaries and autopsy reports of all such cases were retrieved from the database of the DOFM. The DOFM is located in central Sydney and is the primary forensic pathology center in New South Wales (NSW), conducting between 2000 and 2500 autopsies per year during this time period. Permission to inspect the files was

[1]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW, 2052, Australia.
[2]Department of Forensic Medicine, South Western Sydney Local Health District, PO Box 90, Glebe, NSW, 2037, Australia.
[3]School of Medical Sciences, University of New South Wales, Sydney, NSW, 2052, Australia.
[4]Sydney Medical School, University of Sydney, NSW, 2008, Australia.
*The National Drug and Alcohol Research Centre at the University of NSW is supported by funding from the Australian Government.

Received 18 Dec. 2012; and in revised form 25 April 2013; accepted 24 May 2013.

received from the Sydney Local Health District Human Research Ethics Committee. All cases were reviewed by the authors.

In NSW, a case must be reported to the coroner where a person dies a violent or unnatural death. The majority of such cases undergo a standardized forensic autopsy, with examination of all major organs and quantitative toxicological analysis. Cause of death is determined by the forensic pathologist on the basis of circumstances of death, the autopsy findings, and the toxicological analyses. Circumstances of death, and case histories, were obtained from accompanying police reports to the coroner.

Toxicological Analyses

All autopsy blood samples were taken peripherally (femoral or subclavian vessels). Toxicological data were reported for alcohol, cannabis (determined by the presence of Δ-9-THC), opioids (e.g., morphine, methadone, buprenorphine, oxycodone, hydrocodone, tramodol), psychostimulants (methamphetamine, cocaine, benzoylecgonine, 3,4methylenedioxymethamphetamine [MDMA]), benzodiazepines (e.g., diazepam, oxazapam, temazepam, flunitrazepam, alprazolam), gammahydroxybutyrate (GHB), antidepressants (e.g., amitriptyline, citalopram, moclobemide, venlafaxine, sertraline, dothiepin, imipramine, fluoxetine), and antipsychotic medications (e.g., thioridazine, chlorpromazine, olanzapine, lithium). In cases where there was prolonged hospitalization prior to death, antemortem toxicology taken at admission was reported, and drugs administered by hospital and medical staff excluded. All samples were screened by immunoassay and either by gas chromatography or by high-performance liquid chromatography (HPLC) for drugs of abuse and common therapeutic substances. All analyses of blood were conducted by the Forensic Toxicology Laboratory of the NSW Forensic & Analytical Science Service (formerly the Division of Analytical Laboratories).

Urine samples taken at autopsy were screened for AAS metabolites by the Australian Sports Drug Testing Laboratory, using gas chromatography and mass spectrometry, there being no current blood test. In addition, abnormalities in steroid profiles were examined for evidence of exogenous testosterone use, with a testosterone/epitestosterone ratio of >4 considered evidence of exogenous use by the Australian Sports Drug Testing Laboratory (23). As is the case in other forensic institutes (11,12), AAS are not routinely screened for by the NSW Forensic & Analytical Science Service. Such tests are conducted at the request of the forensic pathologist when there are signs (e.g., a pronounced, overdeveloped musculature), or circumstances indicating suspected AAS use (e.g., substances discovered at the death scene). It should be noted that the field of AAS use, and the detection of such use, is in constant flux as new drugs are developed, and testing menus are likely to vary over time.

Statistical Analyses

For continuous distribution means, standard deviations (SD) and ranges were reported. All analyses were conducted using SPSS Statistics, 20.0 (24).

Results

Case Characteristics

A total of 24 cases were identified, all male, with a mean age in their early thirties (Table 1). The majority were in a sexual relationship. Two-thirds were employed, the most common occupations being security guard (n = 5) and personal fitness trainer (n = 4). Bodybuilding was noted in a fifth of cases. The mean BMI was 29.6 kg/m^2, with 45% exceeding the cutoff for obesity (>30 kg/m^2). Evidence of recent injecting drug use was noted in 54.2% of cases. Two cases were hepatitis C virus (HCV) positive, and one was HIV positive on serologic testing.

TABLE 1—*Characteristics of cases of sudden or unnatural death in which anabolic-androgenic steroids were detected.*

	(N = 24)
Age (mean years)	31.7 years (SD 6.8, range 22–48 years)
Sex (% male)	100%
Marital status (%)	
Single	45.8% (11)
Married/cohabiting	25.0% (6)
In relationship	29.2% (7)
Employment status	
Employed	66.7% (19)
Unemployed	16.7% (4)
Student	4.2% (1)
Bodybuilder	20.8% (5)
BMI (mean)	29.6(SD 3.8, range 22.2–39.9)
Death particulars	
Accidental drug toxicity	54.2% (13)
Combined accidental drug toxicity/cardiovascular disease	8.3% (2)
Suicide	16.7% (4)
Homicide	12.5% (3)
Accident	4.2% (1)
Undetermined	4.2% (1)

The most common direct cause of death was drug toxicity which, in conjunction with combined drug toxicity/cardiovascular disease, constituted two-thirds of cases. Psychostimulant toxicity was the direct cause of death in eight cases (33.3%) and opioid toxicity in 7 (29.2%). Arsenic poisoning was diagnosed in one case – the manner of death in this case was not able to be determined, but homicide was suspected. Violent death (suicide, homicide) constituted a quarter of cases. Three of the four suicides were by gunshot, with one hanging. All three definite homicides were gunshot victims. The sole accidental death was of a pilot of a light aircraft with controlled flight into terrain, situational unawareness being the likely cause of the crash. There were no deaths solely attributable to natural causes.

Toxicology

Abnormal testosterone/epitestosterone ratios >4 were reported in 15 of 24 cases, indicative of exogenous testosterone use, the most common indicator of AAS, followed by with metabolites were of nandrolone, stanozolol, and methandienone (Table 2). In one case, a significantly increased concentration of dehydroepiandrosterone was reported. Tamoxefin was also present, a drug frequently used in AAS steroid cycles (25). The presence of increased dehydroepiandrosterone and of tamoxifen in this case is strongly suggestive of exogenous steroid use. Nandrolone may be present in low concentrations in urine from exogenous and endogenous sources. We did not have access to more detailed data on nandrolone concentrations or specific metabolites. In 12 of these 14 cases, however, metabolites of other AAS were detected and/or increased testosterone/epitestosterone ratios, consistent with AAS use, while in the remaining two cases, other evidence of AAS use was noted.

TABLE 2—*Toxicology of cases of sudden or unnatural death in which anabolic-androgenic steroids were detected.*

	(*N* = 24)
Abnormal testosterone/epitestosterone ratio	62.5% (15)
Anabolic-androgenic steroid metabolites	
Nandrolone	58.3% (14)
Stanozolol	33.3% (8)
Methandienone	20.8% (5)
Boldenone	8.4% (2)
Trenbolone	4.2% (1)
Dehydroepiandrosterone	4.2% (1)
Metenolone	4.2% (1)
Oxymetholone	4.2% (1)
Psychostimulants (%)	66.7% (16)
Cocaine	41.7% (10)
Methamphetamine	37.5% (9)
MDMA	16.7% (4)
Opioids (%)	37.5% (9)
Morphine	37.5% (9)
Codeine	25.0% (6)
Oxycodone	8.4% (2)
Tramadol	4.2% (1)
Pholcodine	4.2% (1)
Cannabis (%)	0.0% (0)
Alcohol (%)	25.0% (6)
Benzodiazepines (%)	45.8% (11)
Diazepam	29.2% (7)
Alprazolam	20.8% (5)
Oxazepam	8.4% (2)
Temazepam	8.4% (2)
Flunitrazepam	4.2% (1)
Antidepressants (%)	4.2% (1)
Venlafaxine	4.2% (1)

TABLE 3—*Major autopsy findings of cases of sudden or unnatural death in which anabolic-androgenic steroids were detected.*

Pathology	(*n* = 23)
Steroid-related pathology	
Testicular atrophy*	45.8% (11)
Testicular fibrosis	43.5% (10)
Arrested spermatogenesis	47.8% (11)
Cardiac	
Left ventricular hypertrophy	30.4% (7)
Moderate–severe atherosclerotic occlusion	26.1% (6)
Fibrosis	
Myocardial fibrosis	13.0% (3)
Interstitial fibrosis	8.7% (2)
Perivascular fibrosis	13.0% (3)
Cardiomyopathy	4.3% (1)
Myocarditis	8.7% (2)
Myocyte necrosis	13.0% (3)
Hepatic	
Cirrhosis	8.7% (2)
Fibrosis (excluding cirrhosis)	4.3% (1)
Steatosis (moderate–severe)	8.7% (2)
Hepatomegaly	13.0% (3)
Pulmonary	
Bronchopneumonia	21.7% (5)
Bronchitis	8.7% (2)
Birefingement material	25.0% (6)
Emphysema	4.3% (1)
Renal	
Nephrosclerosis	8.7% (2)
Fibrosis	8.7% (2)

*n = 24.

Blood toxicology was available for all cases. In all but one case (95.8%), psychoactive substances other than steroids were detected. The most prevalent substances were psychostimulants, present in two-thirds of cases. Opioids were detected in 37.5% of cases, with morphine present in all these cases. A quarter had alcohol detected, with a mean concentration of 0.093 g/100 mL (SD 0.095, range 0.010–0.247 g/100 mL). Benzodiazepines were detected in nearly half of cases, most commonly diazepam. Venlafaxine was present in one case, as was ketamine, while no case tested positive for cannabis.

Autopsy Findings

Muscular physique was noted in 21 cases (87.5%). In nearly half of cases, testicular atrophy, testicular fibrosis, and arrested spermatogenesis were noted (Table 3). No case exhibited gynecomastia, acne, or prostate enlargement.

Cardiac pathology was diagnosed in 11 cases (47.8%). The mean heart weight was 467.7 g (SD 107.7, range 304–760 g), with left ventricular hypertrophy present in seven cases (30.4%). Moderate to severe stenosis (>50%) of the coronary arteries was diagnosed in a quarter of cases. Fibrosis of the myocardium was noted in three cases (13.0%). Psychostimulants were present in all six cases who exhibited moderate–severe coronary artery stenosis, 6 of 7 cases of left ventricular hypertrophy, 2 of 3 cases of fibrosis of the myocardium, 1 of 1 case of cardiomyopathy, 2 of 3 cases of myocyte necrosis, and 2 of 2 cases of myocarditis.

Clinically significant hepatic pathology was diagnosed in six cases (26.1%). Two cases had cirrhotic livers, one of which was HCV positive on serological testing. Pulmonary edema was present in 16 cases (69.4%), 14 of which were drug overdoses. Pulmonary vascular birefringent material (indicating probable injection of tablet preparations or other insoluble materials) was detected in a quarter of cases. Other pulmonary pathology was noted in six cases (26.1%), most commonly bronchopneumonia. Renal pathology was diagnosed in three cases (13.0%). No preexisting intracranial pathology was identified, and there were no tumors typically associated with AAS use.

Discussion

The cases in this series were exclusively male and aged on average in their early thirties, characteristics consistent with earlier case studies and series (7,11–13,15–17). There was extensive physical evidence of steroid abuse, most notably testicular atrophy, and fibrosis, as well as arrested spermatogenesis. Muscular overdevelopment was present in almost all cases, with half having BMIs in the obese range. As reported elsewhere (4), these high BMIs were not due to obesity, but to muscle volume and density. A large proportion of cases were employed as security guards or as personal trainers, occupations in which AAS may offer professional advantage.

Exogenous testosterone appeared to be the most frequent form of AAS use, as evidenced by metabolites of nandrolone, stanozolol, and methandienone. An outstanding feature of these cases was their extensive polypharmacy. All but a single case had psychoactive substances other than AAS detected in blood, and death was due to drug toxicity nearly two-thirds. Half were injecting substances other than steroids, and a quarter showed evidence of likely injection of tablet preparations. Most prominent were the psychostimulants, although opioids were also prevalent. In terms of the latter, in eight of the nine morphine positive cases, the evidence was of the injection of opioids and of heroin in particular. In one case, it would appear that a codeine preparation was consumed. It is clear that there is a strong association between the illicit use of AAS and the illicit use of other substances, and with

injecting drug use more broadly. As is commonly seen among psychostimulant and opioid users (26), there was widespread use of benzodiazepines. In contrast, no case was positive for cannabis, consistent with reports elsewhere of low rates of cannabis use (20–22). This is clearly not a drug that appeals to this population, who appear to prefer injectables.

While there were no deaths solely attributable to natural causes, an outstanding feature of these cases was widespread cardiovascular disease. These findings are consistent with earlier work associating AAS use with such pathology (1,12–19). The etiology of these pathologies is uncertain, however, given the extensive use of psychostimulants seen in this and other studies (20–22), and that both AAS and psychostimulants are associated with similar pathology. Certainly, as noted above, there were other physical manifestations of steroid abuse. The majority of cases who exhibited cardiovascular disease were, however, positive for psychostimulants. It may be that the combination of AAS and psychostimulants increases the risk of cardiovascular disease.

Finally, death from violence occurred in over a quarter of these cases, similar in proportion to the few case series conducted to date (11,12). As noted earlier, AAS use is associated with increased aggressiveness and depression (1,11,12). The association with illicit drug use may also be of relevance here, as death due to homicide and suicide comprises a significant proportion of fatalities among psychostimulant and opioid users, and with injecting drug use more generally (27).

As in all studies, caveats must be made. AAS are not routinely screened, but conducted where there is reason by the forensic pathologist to suspect AAS use, as is the case in other cases series (11,12). It is thus possible that there were undetected cases not contained in this series, particularly there were no overt reasons to order such tests, for example, no pronounced muscularity or AAS found at the death scene. Finally, the field of AAS use, and the detection of such use, is in constant flux as new compound is developed, and new test is required to detect them. Again, it is possible that cases have not been detected. In relation to this, and the previous point, it must be noted that this is not an epidemiological study, but a clinical study of case presentations where such drugs have been detected. The data also do not allow us to determine the length and severity of AAS use among cases, nor their polypharmacy histories. Such data would be useful in attributing causation to the cardiovascular disease seen in this series.

In summary, the typical case in this series was a male polydrug user, aged in their early thirties, with drug toxicity the being most common cause of death. Extensive cardiovascular disease was a particularly notable feature.

Acknowledgments

The authors wish to thank Vera Alderton and Briony Larance for their assistance.

References

1. Karch SB. Karch's pathology of drug abuse, 4th edn. Boca Raton, FL: CRC Press, 2009.
2. Brennan BP, Kanayama G, Hudson JI, Pope HG. Human growth hormone abuse in male weightlifters. Am J Addict 2011;20:9–13.
3. Copeland J, Peters R, Dillon P. Anabolic-androgenic steroid use disorders among a sample of Australian competitive and recreational users. Drug Alcohol Depend 2000;60:91–6.
4. Kao TC, Deuster PA, Burnett D, Stephens M. Health behaviors associated with use of body building, weight loss, and performance enhancing supplements. Ann Epidemiol 2012;22:331–9.
5. Larance B, Degenhardt L, Copeland J, Dillon P. Injecting risk behaviour and related harm among men who use performance- and image-enhancing drugs. Drug Alcohol Rev 2008;27:679–86.
6. Petersson A, Bengtsson J, Voltaire-Carlsson A, Thiblin I. Substance abusers' motives for using anabolic androgenic steroids. Drug Alcohol Depend 2010;111:170–2.
7. Di Paolo M, Agozzino M, Chiara T, Luciani AB, Bassi A, Molendini L, et al. Sudden anabolic steroid abuse-related death in athletes. Int J Cardiol 2007;114:114–7.
8. Hakansson A, Mickelsson K, Wallin C, Berglund M. Anabolic androgenic steroids in the general population: user characteristics and associations with substance use. Eur Addict Res 2012;18:83–90.
9. Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope HG. Treatment of anabolic-androgenic steroid dependence: emerging evidence and its implications. Drug Alcohol Depend 2010;109:6–13.
10. Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope HG. Anabolic–androgenic steroid dependence: an emerging disorder. Addiction 2009;104:1966–78.
11. Petersson A, Garle M, Granath F, Thiblin I. Morbidity and mortality in patients testing positively for the presence of anabolic androgenic steroids in connection with receiving medical care. A controlled retrospective cohort study. Drug Alcohol Depend 2006;8:215–20.
12. Thiblin I, Lindquist O, Rajs J. Cause and manner of death amongst users of anabolic androgenic steroids. J Forensic Sci 2000;45:16–23.
13. Petersson A, Garle M, Holmgren P, Druid H, Krantz P, Thiblin I. Toxicological findings and manner of death in autopsied users of anabolic androgenic steroids. Drug Alcohol Depend 2006;81:241–9.
14. Baggish AL, Weiner RB, Kanayama G, Hudson JI, Picard MH, Hutter AM, et al. Long-term anabolic-androgenic steroid use is associated with left ventricular dysfunction. Circ Heart Fail 2010;3:472–6.
15. Fineschi V, Baroldi G, Monciotti F, Reattelli LP, Turillazzi E. Anabolic steroid abuse and cardiac sudden death. A pathologic study. Arch Pathol Lab Med 2001;125:253–5.
16. Fineschi V, Riezzo I, Centini F, Silingardi E, Licata M, Beduschi G, et al. Sudden cardiac death during anabolic steroid abuse: morphologic and toxicologic findings in two fatal cases of bodybuilders. Int J Legal Med 2007;121:48–53.
17. Montisci M, El Mazloumn R, Cecchettom G, Terranova C, Ferrara SD, Thiene G, et al. Anabolic androgenic steroids abuse and cardiac death in athletes: morphological and toxicological findings in four fatal cases. Forensic Sci Int 2012;217:e13–8.
18. Wysoczanski M, Rachko M, Bergmann SR. Acute myocardial infarction in a young man using anabolic steroids. Angiology 2008;59:376–8.
19. Denham BE. Association between narcotic use and anabolic-androgenic steroid use among American adolescents. Subst Use Misuse 2009;44:2043–61.
20. Dodge T, Hoagland MF. The use of anabolic androgenic steroids and polypharmacy: a review of the literature. Drug Alcohol Depend 2011;114:100–9.
21. Garevik N, Rane A. Dual use of anabolic-androgenic steroids and narcotics in Sweden. Drug Alcohol Depend 2010;109:144–6.
22. Skarberg K, Nyberg F, Engstrom I. Multisubstance use as a feature of addiction to anabolic-androgenic steroids. Eur Addict Res 2009;15:99–106.
23. Mareck U, Geyer H, Fussholler G, Schwenkem A, Haenelt N, Piper T, et al. Reporting and managing elevated testosterone/epitestosterone ratios-novel aspects after five years' experience. Drug Test Anal 2010;2:637–42.
24. IBM. SPSS statistics, 20.0. Chicago, IL: IBM, 2011.
25. Baker JS, Graham MR, Davies B. Steroid and prescription medicine abuse in the health and fitness community: a regional study. Eur J Intern Med 2006;17:479–84.
26. Darke S, Torok M, Kaye S, Ross J, McKetin R. Comparative rates of violent crime amongst regular methamphetamine and opioid users: offending and victimisation. Addiction 2010;105:916–9.
27. Darke S, Degenhardt L, Mattick R. Mortality amongst illicit drug users: epidemiology, causes and intervention. Cambridge, U.K.: Cambridge University Press, 2007.

Additional information and reprint requests:
Professor Shane Darke, Ph.D.
National Drug and Alcohol Research Centre
University of New South Wales
Sydney
NSW 2052
Australia
E-mail: s.darke@unsw.edu.au