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REVIEW ARTICLE

Anabolic steroid abuse: physiological and anaesthetic considerations

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Summary

This review summarises the physiological and pharmacological effects of the anabolic steroids used to enhance performance in sports. The anabolic steroids promote muscle growth and protein synthesis. Side-effects of anabolic steroids include cardiomyopathy, atherosclerosis, hypercoagulopathy, hepatic dysfunction, and psychiatric and behavioural disturbances. It is therefore appropriate that the anaesthetist be familiar with the abuse of anabolic steroids, their potential adverse effects, and the peri-operative risk associated with the use of these drugs.

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The International Olympic Committee (IOC) has banned the use of five classes of substances by athletes: anabolic agents (e.g. steroids), stimulants (e.g. amphetamines), narcotics, diuretics and peptide hormones (e.g. erythropoietin, growth hormone). In recent years, 'doping' (use of ergogenic or performance enhancing drugs) by competitive athletes has reached new levels. However, an increasing number of young people (recreational athletes) are also resorting to these drugs to improve their physique or performance in sports [1].

The aim of this article is to review the pharmacological and physiological aspects of the anabolic steroids and to provide a commentary on the anaesthetic implications of adverse effects of this group of drugs.

History of anabolic steroids

Testosterone was first isolated in 1932. Evidence that anabolic steroids (synthetic derivatives of testosterone that have greater anabolic actions) enhanced physical strength led to experiments conducted on soldiers by Nazi Germany during the Second World War [2].

In the 1950s, the first documented evidence that elite athletes were using anabolic steroids to enhance performance was reported [3]. State funded and supervised programmes supplied anabolic steroids to their athletes in several countries [4]. At the Munich Olympics in 1972, 68% of middle and short distance runners admitted to having used anabolic steroids [5]. This explosion of use of drugs in sport prompted the IOC to develop detection techniques. In 1974, the committee was able to add anabolic steroids to its list of banned substances when drug detection techniques were available. Initial tests relied on the detection of the parent compound using radioimmunoassay techniques. However, rapid and extensive metabolism of the anabolic steroids limited the usefulness of these tests. Metabolites in urine are now tested using mass spectrometry-gas chromatography [6].

Epidemiology

Although elite athletes remain high profile users of anabolic steroids, their use among athletes has probably declined because of improved detection techniques, out of competition testing, and the development of newer performance enhancing drugs that are more difficult to detect (erythropoietin and growth hormone). There is a much larger population of amateur sportsmen, recreational athletes and certain occupational users (such as security guards) who abuse anabolic steroids to improve

Table 1 Reasons for anabolic steroid abuse.

1	Sports	Competitive power sports (athletics, weightlifting, football, rowing, swimming, boxing, cycling)
2	Recreational	Bodybuilding
3	Cosmetic	'Beautiful body' subculture
4	Occupational	Police, Security, Armed forces, Professional sports

their physical appearance [7] (Table 1). Various surveys have estimated that 15–40% of regular gymnasium attendees use anabolic steroids [7–9]. The use of anabolic steroids has increased in youths worldwide. Adolescents are being exposed to anabolic steroid use in schools. Seven percent of US male seniors use anabolic steroids [10]. Current estimates suggest that there are about 3 million anabolic-androgenic steroid abusers in the United States and that about two-thirds of these are non-competitive recreational body builders or non-athletes who use these drugs for cosmetic purposes [11]. Data from the National Household Survey on Drug Abuse in 1991 indicated that the lifetime use of anabolic steroids was 0.9% for males and 0.1% for females. In the United Kingdom, anabolic steroids are the third most common drug offered to children after cannabis and amphetamines [12].

Pharmacology

Testosterone is the main male hormone synthesised in the testis. The hormone is responsible for the secondary sexual characteristics that transform boys into men. In the adult male, testosterone regulates muscle protein metabolism, sexual and cognitive functions, erythropoiesis, plasma lipids, and bone metabolism. Testosterone has approximately equal anabolic and androgenic actions. It is inactive orally because it has a high first pass effect [11].

With the increased use of anabolic steroids over the last 40 years, there has been a parallel increase in the number of different anabolic steroids. Anabolic steroids are synthetic derivatives of testosterone. Maximisation of anabolic and minimisation of androgenic effects, reduced rate of inactivation, altered pattern of metabolism or decreased aromatisation to estradiol are achieved by modification of the testosterone molecule. The 17-α alkylated derivatives of testosterone are relatively resistant to hepatic metabolism and therefore are orally active. Esterification of the 17-β hydroxyl group makes the molecule more soluble in lipid vehicles used for injection. The common anabolic steroids are summarised in Table 2. Testosterone has an anabolic : androgenic ratio of 1, whereas the ratio for nandrolone is 10 and that of stanozolol is 30 (Table 3). However, all anabolic steroids are virilising if administered long enough and at high doses. The anabolic steroids may be administered orally, parenterally by intramuscular injections, and transdermally by topical gel or patch. The active ingredient, testosterone, binds to androgen receptors to exert its androgenic and anabolic actions. It is then reduced in the skin and liver to dihydrotestosterone, which also acts on the androgen receptors. Finally, it is aromatised to estradiol, which has oestrogenic properties.

Table 2 Commonly used anabolic steroids.

17 α alkyl derivatives Oral agents	17 β-ester derivatives Parenteral agents
Methandrostenolone	Testosterone esters: cypionate, enanthate, heptylate, propionate
Methyltestosterone	Nandrolone esters
Oxandrolone	Boldenone
Oxymetholone	Methenolone
Stanozolol	Trenbolone
Ethylestrenol	Dromostanolone
Danazol	
Fluoxymesterone	

Table 3 Anabolic/androgenic ratio of anabolic steroids.

Anabolic steroid	Anabolic/androgenic ratio
Testosterone	1
Methylandrostenediol	2
Oxymetholone	9
Oxandrolone	10
Nandrolone phenpropionate	10
Stanozolol	30

Mechanism of action of anabolic steroids

Testosterone and dihydrotestosterone (DHT) are the main endogenous androgens. Testosterone is produced from cholesterol in the Leydig cells of the testis in the male, and to a lesser extent in the adrenal cortex of both sexes. DHT is derived from testosterone via metabolism by 5α-reductase enzyme. The enzyme is present only in the brain, fat and the male sex organs. DHT is a more potent androgen because it binds to the androgen receptor with greater affinity, but it is present in the plasma at much lower concentration compared with testosterone.

The androgens bind to a cytoplasmic receptor, and the complex then binds to DNA, promoting gene transcription, and then protein translation, which modulates androgen dependent cellular actions [12]. The responses

in different organs vary as a result of different cellular receptor concentration, and enzyme activity of 5α-reductase producing DHT [13, 14].

Synthetic anabolic steroids are a heterogeneous group of compounds with differing affinities for the androgen receptor. The anabolic response to the supra physiological doses taken by athletes is probably mediated by interactions with non-androgen receptors [15]. The anabolic steroids have anticatabolic effects mediated by an inhibitory action on glucocorticoid receptors [16–18].

Skeletal muscle is the primary target tissue of the anabolic steroids. The testosterone induced increase in muscle size is brought about by an increase in muscle protein synthesis leading to a dose-dependent hypertrophy associated with an increase in the cross-sectional area of both type I and type II fibres and an increase in myonuclear number [11, 16]. There is an increase in muscle pennation and this is associated with high force, low velocity muscle contractions. These changes increase muscle strength. Anabolic steroids enhance exercise tolerance and muscle adaptation to overload by protecting against muscle fibre damage and increasing the rate of muscle protein synthesis during recovery. Anabolic steroids enhance collagen synthesis and increase bone mineralisation (via a direct suppression on osteoclasts). Testosterone may enhance anabolism via a direct induction of growth hormone and insulin growth factor-1.

Stanozolol, synthesised in the late 1950s, is twice as active as an anabolic agent, and one third as active as an androgen compared with testosterone [19]. Nandrolone has a predominant anabolic effect in skeletal muscle [20] (Table 3).

In 2003, the FDA became aware of a substance called tetrahydrogestrinone (THG), which was used by athletes to improve their performance. THG is a 19-nor steroid and structurally related to gestrinone (used for the treatment of endometriosis). It is a potent androgen and progestin (progesterone receptor agonist) but lacks oestrogen activity. THG is more potent than nandrolone (the most widely abused androgen in sports doping) and trenbolone (the most potent synthetic androgen known). Because of its potent androgen and progesterone actions, it can suppress the hypothalamic-pituitary axis, leading to testicular atrophy and reduced spermatogenesis in men as well as androgen withdrawal effects when the drug is ceased. At high doses it can cause hypomania. In women, THG causes virilisation, anovulation, infertility and menstrual disturbances. In children, it causes early epiphyseal closure and reduced height. Hepatotoxicity is a potential complication [21].

Table 4 Drugs commonly used in combination with steroids.

Drug/supplement	Reason for use
Diuretics	Masking agents; reduce oedema
Tamoxifen	Prevents gynaecomastia
Thyroxine	Increases basal metabolic rate.
Human growth hormone	Anabolic effects, increase muscle mass and strength
Insulin	Anabolic, increase muscle mass
Insulin like growth factor	Anabolic, increase muscle mass
Beta blockers	To reduce tremors
Ephedrine	Stimulant, fat loss
Clenbutarol	Stimulant, fat loss
Amphetamine	Stimulant, fat loss
Opioids	Analgesia
Creatine	Ergogenic supplement

Dosing schedules

Dosing schedules revolve around a programme of cycling, stacking and pyramiding [11, 22]. Cycles of steroid use of 4–12 weeks are used with complete abstinence in-between in an attempt to minimise side-effects and receptor down regulation. Stacking refers to the use of more than one steroid within a cycle to avoid tolerance. Pyramiding refers to the escalating dosing regimen of the anabolic steroids, initially at approximately therapeutic doses, but as the cycle progresses, doses are markedly increased (often 100–1000 times therapeutic dose). Towards the end of the cycle, doses are tapered off to avoid any withdrawal symptoms [3]. Approximately 90% of anabolic steroid abusers use a variety of other 'muscle-shaping' drugs (e.g. diuretics, thyroxine, and growth hormone) in addition to stacking different types of steroids. These accessory drugs and dietary supplements can be potentially more toxic than the anabolic steroids (Table 4).

Adverse effects of anabolic steroids

The most common reported side-effects were increased libido (61%), changes in mood (48%), reduced testicular volume (46%), and acne (43%). Gynaecomastia and abnormal liver function tests was also a common finding. Despite these effects, only 19% reported that they would not use anabolic steroids in the future [23]. Women athletes tolerate the side-effects of anabolic steroids such as facial hair, aggressiveness, deepening of the voice, and clitoral enlargement [24].

Cardiovascular adverse effects

Adverse cardiovascular effects induced by anabolic steroids include hypertension, left ventricular hypertrophy, impaired diastolic filling, polycythaemia, and thrombosis.

Although the incidence of anabolic steroid induced adverse cardiovascular effects is unknown, anaesthetists and surgeons should be aware of the increased perioperative risks in anabolic steroid abusers who are undergoing elective surgery.

There are several case reports of sudden death associated with exercise among anabolic steroid abusers [25–30]. Weight training and exercise induce ventricular hypertrophy. Some studies suggested that myocardial hypertrophy was more extensive in athletes who used anabolic steroids in addition to exercise [31, 32]. However, a case series study reported that the echocardiographic measurements of left ventricular hypertrophy (LVH) in weight lifters who used anabolic steroids were not different from those did not use them [33]. Ventricular hypertrophy causes impaired isovolumetric relaxation, diastolic dysfunction and fractional shortening [30].

Focal areas of myocardial fibrosis are commonly found at autopsy among anabolic steroid users [26, 27, 30, 34]. It is suggested that focal myocardial fibrosis is caused by rapid myocardial fibre growth outstripping its blood supply, resulting in piecemeal necrosis and subsequent fibrosis [27]. A direct cellular toxic mechanism mediated by disturbances of ion fluxes, and loss of membrane integrity (leading to cell death and fibrosis) has been suggested [14, 35]. These changes are irreversible. The fibrotic areas can potentially act as a focus for a malignant arrhythmia, or if extensive, cause cardiomyopathy.

Animal studies have shown that anabolic agents enhance the pressor response to catecholamines, mediated by inhibition of extraneuronal uptake of neuroamines, and increased vascular response to norepinephrine [36]. These changes may contribute to malignant arrhythmias and cause sudden death during periods of exertion.

Lipids

It has been consistently shown that anabolic steroid use is associated with abnormal lipid profiles: a decrease in high-density lipoprotein cholesterol and a variable increase in low density lipoprotein cholesterol and total cholesterol [37, 38]. This lipid profile is associated with an increased risk of atheromatous coronary artery disease.

Vascular thrombosis

Acute vascular thromboses in coronary [26, 29, 39, 40], cerebral [41] and peripheral blood vessels [42, 43] have been reported in anabolic steroid users. A weight lifter who suffered a myocardial infarction had normal coronary arteries (on angiography) although he had hypercholesterolaemia [39]. In another patient who died as a result of a myocardial infarction, the coronary arteries were free of atheroma at post mortem [29]. It was suggested that coronary vasospasm contributed to the myocardial infarction in these cases.

An occlusion of the middle cerebral artery (confirmed on angiography) occurred in a 34-year-old body builder [41]. There was no evidence of a mural thrombus in the heart chambers on echocardiography. These findings suggested a hypercoaguable state resulting from his anabolic steroid use. Left ventricular mural thrombi were present in two patients with global ventricular dysfunction who presented with acute embolic ischaemia of the lower limbs [43].

Although platelet counts are normal in anabolic steroid abusers, platelet aggregation is increased. This is possibly caused by an increased production of thromboxane in platelets, and a decreased prostacyclin production in vessel walls [44–46]. Indirect mechanisms, such as increased low-density lipoprotein cholesterol concentrations that are associated with anabolic steroid abuse, may increase platelet sensitivity [44]. Androgens increase the production of procoagulant factors such as factors VII and IX [47]. Increased vascular reactivity associated with the anabolic steroids is mediated by impaired nitric oxide activity [48].

Hyperhomocysteinaemia is an independent risk factor for atherosclerosis. Bodybuilders using anabolic steroids in a cyclical fashion induce acute hyperhomocysteinaemia during the build up phases of the cycle [49]. The combination of hyperhomocysteinaemia and the abnormal lipid profile associated with anabolic steroid use increases the risk of atherosclerotic plaque formation.

Hepatotoxicity

There are numerous reports of liver dysfunction associated with anabolic steroid use. These include asymptomatic elevations in serum aminotransferases, cholestasis, peliosis hepatitis (an uncommon condition characterised by small blood filled cystic spaces distributed throughout the liver parenchyma), hepatocellular carcinoma, hepatic adenomas, and hepatic haematomas [50–53]. Hepatotoxicity is usually associated with the C17 alkylated compounds such as stanozolol [54, 55].

Tendon injury

Anabolic steroids predispose to tendon rupture by altering collagen structure. The changes in collagen cause the tendons to become stiffer and less elastic. Tendon strength is unchanged. It is possible that the increased muscle contractile strength is not matched by slower adapting tendons, so that the tendons are the weakest link in the system.

Neuropsychiatric effects

The early behavioural effects of the anabolic steroids include elevation in confidence, energy and enthusiasm.

Libido is increased. With larger doses, users become disinhibited, lack judgement, and are prone to mood swings. Occasionally, anabolic steroid abusers act on their aggressive feelings resulting in violent, antisocial behaviour ('road rages') [56–58]. Approximately 5% of anabolic abusers experience manic or hypomanic reactions. Anabolic steroids induce drug dependent behaviour, and withdrawal symptoms when the drugs are discontinued [59]. Withdrawal symptoms, such as reduced muscle size and strength, fatigue, depressed mood and decreased libido, are present in about 88% of anabolic abusers and cause 'craving' (a desire to resume anabolic steroid abuse) and habituation.

Reproductive system

Large doses of exogenous androgenic agents induce a pituitary hypogonadal state, associated with decreased secretion of follicular stimulating hormone and luteinising hormone. This can persist for weeks after the discontinuation of the androgenic agent [60]. In the male, this causes a decrease in testicular size, with a decreased production of sperm, which have abnormal morphology and motility. Gynaecomastia occurs in about 40% of male users as a result of the metabolism of the anabolic steroids to oestradiol (which stimulates mammary tissue growth) by hepatic aromatase enzymes [3]. Masculinisation occurs in females, leading to menstrual irregularities, clitoral enlargement, hirsutism, deepening of voice, oily skin and breast atrophy. Of these, clitoral enlargement and voice changes are usually permanent [55].

Dermatological changes

Acne is a common finding among steroid users of both sexes and results from hypertrophy of the sebaceous glands, which increases skin surface lipids and the cutaneous population of *propionibacteria acnes*. Male pattern baldness, cutaneous striae, alopecia, and hirsutism may be present. Repeated injections cause fibrosis, dystrophic calcification and oil granuloma at the injection sites.

Long-term effects

The long-term consequences result from the anabolic steroid effects on the cardiovascular system, mental health issues and the possible increase incidence of neoplasms [61]. The risk of mortality among anabolic steroid abusers is approximately four times higher than non-abusers. There are case reports linking anabolic steroids with hepatic cancer, renal carcinoma and testicular tumours [50–54]. Complications associated with the use of parenteral anabolic steroids include bacterial abscesses, septic arthritis, septicaemia and blood-borne infections such as hepatitis B, hepatitis C and human immunodeficiency virus [11].

Clinical evaluation of the patient

Young men who undertake weight training, bodybuilding or sports that require power and strength are at high risk for anabolic steroid abuse. Evaluation of a potential, suspected or known anabolic abuser includes a specific history, physical examination and laboratory investigations.

History

Anaesthetists should be aware of the potential problems in managing steroid users in the peri-operative period. As part of this, an accurate history should be taken including drugs, doses and timing in their cycle in those who are suspected of taking steroids. The drug history should be taken in a systematic manner. The use of nutritional supplements and 'accessory' drugs (e.g. ephedra, insulin, growth hormone) should be excluded.

Physical signs

There are several physical signs that may indicate anabolic steroid abuse. In a muscular athlete, acne, gynaecomastia and cutaneous striae in the deltopectoral area are frequently present. Needle stick marks in the thighs, buttocks or deltoid would further support the diagnosis of anabolic steroid abuse. The female anabolic steroid abuser may have muscular hypertrophy, hirsutism, male-pattern baldness, breast tissue atrophy, clitoral hypertrophy or voice deepening.

Laboratory investigations

The pre-operative work-up should include the laboratory investigations summarised in Table 5.

Anaesthetic considerations

Physiological considerations

Large muscle mass and high caloric intake can lead to high ventilatory requirements caused by increased oxygen

Table 5 Abnormal laboratory tests in anabolic steroid abusers.

Blood count	Increased haemoglobin, haematocrit
Liver function tests	Increased ALT, AST.
Plasma cholesterol	Increased high-density lipoprotein cholesterol
Electrocardiogram	Left ventricular hypertrophy
Echocardiogram	Impaired diastolic function
Hormone concentrations	Decreased LH, FSH Increased testosterone (on anabolic steroid) Decreased testosterone (during withdrawal)
Urine analysis	Positive for anabolic steroids and its metabolites and other supplements
Semen analysis	Decreased sperm count and motility

ALT = alanine transaminase, AST = aspartate transaminase; LH = luteinising hormone; FSH = follicle-stimulating hormone.

consumption and carbon dioxide production. Sellers reported a patient (bodybuilder) who developed an excessively high end-tidal carbon dioxide level following the fasciculations associated with succinylcholine and subsequently needed higher than expected ventilatory requirements [62]. Increased muscle mass has been linked to the rapid development of a compartment syndrome in a trauma patient [63].

Fluid and electrolyte imbalances are common among anabolic steroid users. The anabolic steroids have a mineralocorticoid effect. Diuretics are often combined with the steroid to mask these effects.

The cardiovascular changes associated with anabolic steroid abuse can potentially cause serious problems. Left ventricular hypertrophy can cause significant diastolic dysfunction. Transoesophageal echocardiography may be useful to guide fluid balance. There is a risk of arrhythmias caused by re-entrant circuits associated with the fibrotic areas within the myocardium.

Prophylaxis against deep vein thrombosis is essential in the peri-operative period because of the increased risk of thromboembolism.

Pharmacological changes

Resistance to non-depolarising neuromuscular blocking drugs has been reported in anabolic steroid abusers [64]. The mechanisms of this altered response include an increased volume of distribution caused by water retention associated with anabolic steroid use and an increased number of acetylcholine receptors associated with the increased muscle mass. Although succinylcholine is not contraindicated, excessive and vigorous muscle fasciculations may occur.

Oral anabolic steroids induce hepatic enzymes more than parenteral ones. This is important and higher doses of anaesthetic agents may be required. However, sensitivity to oral anticoagulants and oral hypoglycaemic agents is increased and care should be taken when these drugs are used [65].

There are also potential problems caused by other medications (such as thyroxine, diuretics, beta blockers and sympathomimetics) used with the anabolic steroids. Anabolic steroids have a potential to cause physical and psychological dependence. A recent case report highlighted the anabolic-androgenic steroid withdrawal problems in a weight lifter who was abusing anabolic steroids [66]. The patient underwent aortic valve replacement surgery and the postoperative course was complicated because the patient could not breathe spontaneously for 21 days. The patient recovered immediately after the intramuscular administration of testosterone esters. The discontinuation of long-term anabolic steroid use can cause unexpected withdrawal symptoms in addition to the endocrine hypofunction [65].

Despite legislation, the illegal use of high doses of anabolic steroid for enhancing athletic performance and for cosmetic reasons remains prevalent. It is therefore appropriate that the anaesthetist be familiar with the abuse of anabolic steroids, their potential adverse effects, and the peri-operative risk associated with the use of these drugs.

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