Anabolic-Androgenic Steroids; Ergogenic and Cardiovascular Effects

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1. INTRODUCTION

Testosterone is the natural endogenous male hormone and is produced primarily by the testes. It was first isolated and chemically characterised in 1935 [1] and is responsible for both the masculinising (androgenic) and tissue building (anabolic) effects associated with male adolescence and adulthood. Since this time there have been many pharmacological attempts to manufacture a steroid agent capable of producing only the anabolic effect of these compounds. Despite the fact that some synthetic derivatives of testosterone do possess a greater anabolic than androgenic action, such a steroid has not been developed. The inability to separate the actions of these preparations suggests that distinct androgenic and anabolic receptors do not exist or that they have yet to be isolated [2]. For this reason the natural forms of testosterone and its synthetic derivatives are usually classified as anabolic-androgenic steroids (AAS).

The use of AAS by athletes was prompted by dramatic improvements in performance of several weightlifting squads at the 1954 world championships. Androgens were rumoured to be responsible and this led many more competitors to use them in athletic events at the 1956 Melbourne Olympic Games. The scale of misuse had escalated to an estimated 68% of all athletes in short and middle distance running and field events at the 1972 Munich Olympics [3]. This purported widespread use of AAS, and the development of assay techniques capable of detecting metabolites of these compounds in urine and blood, led to the inclusion of AAS on the list of banned substances for the 1976 Olympic Games in Montreal.

Before continuing with this review, it is pertinent to highlight two caveats. Firstly, of all the substances banned by the International Olympic Committee, AAS only account for about 15% of all positive drug tests, and secondly the presence of AAS in the world of competitive athletics constitutes a small portion of the total population that misuse these substances. With this in mind, this paper will review the AAS preparations commonly misused by athletes, examine the question of the efficacy of their performance enhancement and the mechanisms responsible. In addition, the associated cardiovascular ramifications of their use will be discussed and avenues for future research suggested.
### 2. ANABOLIC-ANDROGENIC PHARMACOLOGY

There are approximately 30 drugs that can be classified as AAS. The commonly used preparations are itemised in Table 1 and the route of administration stated [4-7]. Despite their similarity to testosterone, these products are structurally modified. This is necessary, as testosterone cannot be administered effectively either orally or intramuscularly. When given orally, testosterone is rapidly absorbed into the portal circulation and subjected to 'first pass' degradation by the liver, such that only a small concentration enters the systemic circulation. Testosterone taken intramuscularly is also rapidly absorbed from the injection medium and degraded to leave little active compound in the plasma. Structural modification of the testosterone molecule to produce AAS slows the rate of absorption and catabolism and therefore maintains greater steroid concentrations for longer periods [8].

Table 1.
Commonly used oral and intramuscular AAS.

<table>
<thead>
<tr>
<th>Oral AAS</th>
<th>Injected AAS</th>
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</thead>
<tbody>
<tr>
<td>Fluoxymesterone (Halotsttin)</td>
<td>Boldenone (Equipoise)</td>
</tr>
<tr>
<td>Methandrostenolone (Dianabol)</td>
<td>Nandrolone decanoate (Deca-durabolin)</td>
</tr>
<tr>
<td>Methenolone (Primobolin)</td>
<td>Testosterone cypionate (Depo-Testosterone)</td>
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<tr>
<td>Methyltestosterone (Metandren)</td>
<td>Testosterone enanthate</td>
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<tr>
<td>Oxandrolone (Anavar)</td>
<td>Testosterone propionate</td>
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<tr>
<td>Oxymetholone (Anadrol)</td>
<td>Testosterone suspension</td>
</tr>
<tr>
<td>Stanozolol (Winstrol)</td>
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</table>

Three general modifications of the molecule allow the above products to maintain their potency in the plasma for longer periods. The oral compounds usually undergo alkylation at the 17 alpha-position with some modification of the ring structure of the steroid. This markedly slows catabolism of the drug. The injected AAS are converted via esterification of the 17 B-hydroxyl group with various carboxylic acids. This renders the compound more lipid soluble in the oil vehicles used for injection, hence slowing the release of the hormone into the circulation. Furthermore, the longer the carbon chain in the ester, the more lipid soluble the steroid becomes, the slower the release into the circulation and the more prolonged the action [9].

Many of the products in Table 1 were developed for the treatment of certain pathologies, for example hypogonadism in adults. The treatment of such disorders requires that the patients are administered these therapies in doses that produce a physiological effect. It has become evident that many of the athletes that misuse these drugs are administering concentrations that may range from 10 to 100 times the levels that have been used pathophysiologically [10]. In addition, athletes rarely use a single preparation, but rather take a cocktail of oral and injectable preparations in various modes (pyramid, stacking) and over cycles of differing durations. These doses and methods are perceived necessary, as the androgen receptor in the
human is saturated or near saturated, and therefore to be effective any exogenous AAS must be taken in pharmacological amounts.

3. ARE ANABOLIC-ANDROGENIC STEROIDS ERGOGENIC?

3.1. Literature Review

Anabolic-androgenic steroids have been used in athletics for over four decades, and have been the subject of much scientific scrutiny. Due to various methodological constraints their ergogenic effect remains equivocal. To address this question scientifically, it is necessary to use a blinded cross-over research design and to standardise the motivation and body composition of subjects involved.

Ariel and Saville [11] subjected a group of experienced weight-trained varsity athletes to a strength training regimen and informed them that the most improved subjects would then receive AAS to enhance their training further. Six subjects were chosen, but were administered with a daily dose of placebo, rather than an AAS, and continued to train. The increase in strength was significantly greater than during the prior training period, suggesting that the perception that they were using AAS produced a psychological state that allowed a greater than expected increase in strength. In addition, some authors have reported difficulty in blinding a protocol due to the side effects of some AAS (acne, testicular atrophy and so on) allowing subjects to break the code. Furthermore, it is difficult to compare many of the published studies, as different AAS drugs, different dosages, different training regimen, different levels of experience of athletes, different diets and different study periods have been used [12]. Consequently, many of the reports in the literature suffer from errors in their design, and therefore their findings are questionable.

Of the studies that have been adequately controlled [for review see 12-14] half report a significant increase in strength during AAS administration, and half observed no strength gains. Again these inconsistencies may be the result of differing assessments of strength (dynamic, static) and the use of trained versus untrained populations. The sample sizes used in many of these studies were also very low, ranging from 3 to 15. In a meta-analysis of previous research, Elashoff et al. [13] reported that in trained athletes slightly greater improvements in strength were observed in the AAS treated group than in placebo with an effect size showing a mean difference of 1 standard deviation. However, these authors stated that given the poor quality of research design, sample size, the lack of a dose-response effect and the tendency for differences to be small in larger studies, these results were questionable, and therefore no firm conclusion concerning the ergogenic potential of AAS is possible.

The inconsistencies in the above results are mirrored by those reported in animal studies. Some studies substantiate the hypothesis that supraphysiological doses of AAS do not affect skeletal muscle [15-17], whereas others report changes in muscle fibre cross-sectional area and protein metabolism [18-21].

In a recent study, the effect of supraphysiological doses of testosterone enanthate (weekly doses of 600 mg for 10 weeks) were investigated [22]. This is a novel study as it more accurately reflects the administration practices used by athletes and bodybuilders. The 43 male subjects were randomly assigned to one of four groups; placebo with no exercise; testosterone with no exercise; placebo with exercise and testosterone with exercise. The intake of energy and total protein and the exercise training regimen were standardised. Following this
intervention period there were significant increases in muscle mass of 3.2 kg in the "testosterone-no-exercise" group, 1.9 kg with "placebo and exercise" and 6.1 kg in the "testosterone and exercise" treatment. Muscle strength increased significantly in all groups except "placebo with no exercise", with an improvement of 38% in the "testosterone-exercise" group. The surprising observation was a 19% increase in muscle strength in the "testosterone-no-exercise" group, as it is usually assumed that an associated exercise stimulus is required before any performance enhancement is observed.

In summary, although there are inconsistencies in the literature regarding the ergogenic effect of AAS, it is evident that when these preparations are administered in supraphysiological doses, the following position stand of the ACSM in 1987 is appropriate; "the gains in muscular strength achieved through high intensity exercise and proper diet can be increased by the use of AAS in some individuals" [23]. However, the results of Bhasin et al. [22] require further confirmation and elucidation of the mechanisms that are responsible for the strength gains observed in the none-exercising group.

3.2. Proposed mechanism of action of AAS

The AAS drugs are thought to mediate their responses in exactly the same manner as other steroid hormones. This process involves interaction with a specific intracellular protein to form a hormone-receptor complex, which in turn is translocated to the nucleus where it attaches on to the nuclear chromatin. This allows the transcription of genes and results in the synthesis of specific messenger RNA molecules. Following ribosomal translation of the code, new proteins are formed which promote a muscle anabolic effect and presumably (based on the previous discussion) an increase in strength.

In addition, it has also been hypothesised that AAS promote a positive nitrogen balance and muscle growth by antagonising the catabolic effect of glucocorticoids [14]. This catabolic effect is normally evident following exhaustive exercise, when concentrations of glucocorticoids are high. This hypothesis is supported by the observation that several androgens are effective inhibitors of the binding of cortisol to the glucocorticoid receptor of skeletal muscle [24]. Thus any myotrophic effect of AAS may be mediated by either or both of these pathways, the latter mechanism being independent of the androgen receptor.

The observation that testosterone administration without any exercise can increase muscle mass and strength [22] suggests that the main mechanism of AAS action is via a messenger RNA mediated increase in protein synthesis. If the anticatabolic effect was the main mechanism, then a group that is not performing exercise should in theory not induce any glucocorticoid catabolism and therefore not require any AAS to antagonise this process.

Increased aggressiveness and altered mood states have been widely reported by athletes and coaches following AAS use. It is popularly believed that androgens can create a psychosomatic state that when channelled correctly may result in increased aggressiveness during competition and increased motivation to perform at greater training intensities. There have been many reports of a relationship between testosterone levels, dominance and aggressive behaviour in animal models [25,26]. In humans this association is less evident with some studies reporting a positive effect and others no relationship [27]. In a recent investigation increases in enthusiasm, aggression and irritability were subjectively observed in subjects administered AAS. However, there were no significant differences recorded between AAS and control groups in response to the Profile of Mood States and Buss-Durkee Hostility Inventory questionnaires, suggesting that the differences were negligible or the
sensitivity of these inventories was not sufficient [28]. In addition anger and aggressiveness profiles were unchanged in subjects receiving weekly doses of 600 mg of testosterone enanthate, compared to placebo groups [22]. It is evident that further investigation is warranted in this area.

Many athletes also report that recovery from intense training is enhanced when associated with AAS administration. This observation could be the result of the anticatabolic effect of AAS in combination with altered mood states, creating a situation of reduced muscle damage and lowered subjective perception of fatigue. This in theory would allow greater training volumes to be achieved which may result in increased performance.

4. CARDIOVASCULAR EFFECTS OF ANABOLIC-ANDROGENIC STEROIDS.

There are many documented side-effects of AAS that include reproductive changes, virilisation and feminisation, liver alterations, metabolic disorders, musculoskeletal injuries, psychiatric complications and cardiovascular effects [29]. Given that many of the adverse reactions to AAS are reversible on withdrawal of the drug, the focus of this section is on the cardiovascular effects, which according to case histories appearing in the literature [e.g. 30-32] are acute and may result in sudden death.

It is known that the use of androgenic-anabolic steroids (AAS) is associated with adverse lipoprotein metabolism. In comparative studies of AAS users with drug free control subjects, it is commonly reported that the concentration of low density lipoprotein cholesterol (LDL\text{c}) is elevated and that of high density lipoprotein (HDL\text{c}) is significantly reduced [4,33,34]. The effect of such preparations on the concentration of total cholesterol (T\text{c}) remains equivocal, with some animal studies reporting an increase [35], but most investigations in humans suggest no change between users and non-users.

The mechanisms responsible for the alterations of serum lipoprotein concentrations by AAS remain unknown. Kantor et al. [36] and Lenders et al. [33] reported that the concentration of hepatic triglyceride lipase (HTGL) (an enzyme that catabolises HDL\text{c}) is increased by up to 300% in bodybuilders self-administering AAS. This increase in HTGL may therefore be responsible for the reduction observed in HDL\text{c} with AAS administration. It is also evident that various anabolic compounds affect the concentration of HTGL by differing amounts. For example, stanozolol, oxandrolone and methyl testosterone increase HTGL whereas testosterone does not [37]. These alterations in lipoprotein metabolism are suggestive of atherosclerosis development, although this has not been supported at autopsy [31].

It is also possible that AAS use may initiate infarction via acute changes in thrombosis and vascular reactivity. An exact cause and effect relationship between AAS and thrombosis has yet to be proven, but it has been suggested that platelet function is altered with their use [38]. Coronary vasospasm or increased vascular reactivity may also contribute to infarction. There is evidence in a male subject self-administering AAS that the nitric oxide dilator system in the forearm vasculature is markedly attenuated [39]. If this were to occur in the coronary circulation, blood flow may be reduced.

A number of studies suggest that cardiac dimensions are altered by the use of AAS. Higher ratio of left ventricular wall thickness to internal diameter, partially impaired diastolic function [40], and increases in left ventricular internal diameter, interventricular septal thickness during diastole and ventricular mass [6] have all been reported in athletes self-administering AAS.
In contrast, at least one study has concluded that AAS do not impair left ventricular function [41].

In summary, AAS may increase the risk of coronary heart disease by altering lipoprotein metabolism, increasing clot formation, changing the reactivity of the endothelium to vasoactive substances or by modulating cardiac dimensions.

5. FUTURE AVENUES OF RESEARCH

It is clear that many questions regarding the ergogenic potential of AAS remain unanswered. The reasons for this are extensive, but include difficulties in standardising research protocols, using appropriate doses and doping regimes. Given the ethical considerations involved, it is evident that this type of research can only be conducted on individuals that self-administer AAS, as only in this cohort do doping practices replicate those observed in the real world. To recruit a group of such subjects and monitor their progress with and without AAS is impractical for the reasons stated earlier.

To attempt to address the question of performance enhancement in these individuals definitively, it may be more beneficial to conduct a series of longitudinal single-subject case studies. With extremely strict monitoring of training loads and diet it would be possible to perform a crossover design with AAS use and non-use during training in the same subject. Although qualitative such a design, if repeated in enough subjects, could answer this ergogenic question. This approach may prove more beneficial in addressing the problem than the usual statistical method, as any enhancement in performance (whether it reaches statistical significance or not) may be practically significant on the track or in the field.

It is important that any possible cause and effect relationship between the use of AAS and coronary heart disease/myocardial infarction be thoroughly examined. Further research must investigate changes in coagulation/fibrinolysis, alterations in vascular reactivity and cardiac injury as a result of AAS misuse. This would serve to protect not only the athletes, but more importantly the many millions of recreational users.

REFERENCES

Discussion: Anabolic-Androgenic Steroids; Ergogenic and Cardiovascular effects

D.A. Cowan:
In your data showing about changing cholesterol and lack of protein concentrations, you had a control group which was separate from the study group, that is, the self-administrators. What happens when these self-administrators come off the steroids? Perhaps you had the chance to investigate that with the individual who you found surreptitiously was using testosterone, but then came off.

N.T. Cable:
The problem with this study is that it was not a crossover design. The data shows that when users come off steroids the HDL and cholesterol changes do revert back to normal. And indeed, in the endothelial study with the one subject, we had measured cholesterol, LDL and HDL prior to testing and observed a return to normal values following withdrawal from testosterone.

D.A. Cowan:
In studies we have done, people who said they were on or were not on were often wrong. We were able to look at samples from them and see where you could detect anabolic steroids or not. And I think one of the problems is how long some of those steroids persist in the body, so they say they have not been using it for some time, but there are still quite measurable quantities of anabolic agents in their bodies.

N.T. Cable:
Some studies report six months to get back to normal.

M. Orme:
You commented on the changes in blood clotting but all your anecdotes were really concerned with myocardial infarction rather than with venous thrombosis. The parallel here is perhaps in the treatment of carcinoma of the prostate where anabolic steroids were commonly given, at least up to a few years ago, and there was a measurable incidence of death due to venous thrombosis. I wondered whether there had been any reports of venous thrombosis or thromboembolism in the individuals you talked about. Many, but not all, of the endothelial effects would be reversed by low dose aspirin. Are there any reports of individuals on the street now starting to use low-dose aspirin to try to prevent some of the adverse effects of anabolic steroids?

N.T. Cable:
In animal models, you seem to get this increase in thrombotic potential. There is also some evidence to suggest it does occur in humans as well. However, I have not heard of any reports of on-the-street people using aspirin to correct these endothelial problems.

J.B. Leiper:
Deaths have been reported in anabolic steroid users. Have you any idea how many deaths have been worldwide? I ask this question because I know of a study carried out in Jersey in
England where a large number of bodybuilders, who chronically used anabolic steroids, have been investigated over a number of years, with no evidence of any anabolic steroid related deaths.

N.T. Cable:
Not all the studies that I mentioned resulted in death. There were three deaths there. I think that worldwide there have been about eight cardiovascular deaths, so we are probably talking about a limited number.

J.B. Leiper:
In the Jersey study some of the individuals have been using steroids since the late 1960s and yet there is no clinical evidence of anabolic steroid related deaths.

N.T. Cable:
If they have been using them since the late 1960s and, presumably, they were in the mid-to late-20s when they started, they are probably now entering the time when cardiovascular disease will be becoming more relevant for that age group. Whether we shall see a greater incidence in that group now relative to the normal population is difficult to say, but it would be worth examining.

A.D. Martin:
I talked to a sprint training coach in Canada who said that he strongly felt that anabolic steroids improved reaction time. I am wondering if you have got a comment on that.

N.T. Cable:
I have often wondered myself about reaction time and whether there is some central effect of these products on arousal such that when the stimulus comes, they react quicker. I personally have not seen any data on that.

T.D. Fahey:
There is a study by Areal done in the 1970s that showed that anabolic steroids affected reaction time and movement time. Nobody is ever really followed up on that and I think that would be a fertile area of research.

A.D. Martin:
The term "aggression" comes up quite frequently in any discussion about anabolic steroids but a very extensive review on aggression and testosterone concluded, after looking at all the animal studies, that there really was not much evidence at all for a relationship.

N.T. Cable:
In humans there is a subjective perception that they feel more aggressive. But when you perform studies with POMS and other questionnaire-related media, you do not find any significant difference between control groups and steroid groups.
J.P. Clarys:
At a certain point in your talk you mentioned isokinetic strength measurements, but you did not come back to it. Maybe you can do it now?

N.T. Cable:
My point was really that the studies that have shown a benefit of these products were the ones that used one-repetition maximum to measure the strength rather than the isometric tests or the isokinetic tests.

O.I. Aruoma:
Do people measure LDL oxidation when evaluating the effects of steroids?

N.T. Cable:
As far as I am aware, people have just measured the lipid profiles without going into any measurements of lipid peroxidation and I think that would be a fruitful area to investigate, in terms of endothelial injury, etc.

P.M. Clarkson:
Years ago, athletes depended on information as it filtered down from journals to scientists to coaches. Now information is almost instantaneously available on the Internet. Athletes can get newly published (or even prior to published) work immediately. Can you comment on that?

N.T. Cable:
I was playing on the Internet preparing for this presentation and I put in "anabolic steroids" and up came a whole host of things. The Muscle Media magazine was there and I went to the bottom of the page, and it recorded the number of hits since February of this year. It was above 83,000 so that is just an indication of the access and a scale of the interest there is in anabolic steroids.