

Review

Doping: a challenge to the endocrinologist. A reappraisal in view of the Olympic Games of 2004

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ABSTRACT

The aim of this review is to provide an update on drug abuse by athletes, their mode of action and the technical difficulties of detection. The most common doping agents are the anabolic steroids (AS), testosterone derivatives modified to take advantage of the anabolic rather than the androgenic properties of the hormone. However, there are numerous side-effects that discourage their use. Several other substances and hormones, GH and rhEPO are currently used alone or combined to enhance performance. The diversity in nature of the substances used requires a constant alertness of physicians to detect drug abuse in sports. Doping is not limited to the professional athletes. It seems to be a generalized phenomenon that reflects modern society's concept of success. Therefore, the campaign to eradicate doping must also focus on individual responsibility. Since modern-day doping is strongly related to hormonal preparations, endocrinologists may play a pivotal role in providing information, protecting athletes' health and, moreover, retaining the ethical value of sport.

Key words: Doping, anabolic steroids, testosterone, GH, rh EPO

*“Εν ἀμίλλαις πονηραίς,
ἀθλιότερος ὁ νικῆσας,”
Ancient Greek saying*

“None so wretched as the competitor who wins victory through cheating”

INTRODUCTION

The impressive development of sport (from Latin “disporto”) in our society during the last few decades

has wide-ranging social, educational and health (“ad salutem servandam”) repercussions¹. Sport may alleviate the pressure that modern society exercises on the mind and body, it enforces self-discipline and ameliorates endurance. “Therefore, sport can bring both fun and fitness to our life”. However, the commercialization of sport has progressively changed this spirit as the desire to win at any cost has overcome all other considerations.

Throughout history, athletes have sought to improve their performance through dietary and medi-

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cal help. Doping is the use of banned pharmacological substances with the unique aim of improving physical performance despite serious adverse effects on health. The word “doping” derives from “dope”, a term describing a primitive alcoholic drink used as a stimulant in South African ceremonial dances². Since success in sport is associated with fame and financial rewards, the use of banned, performance-enhancing agents is highly tempting³. Concerns about ethics and controversy over the safety of doping among elite athletes first appeared during the 1920s and 1930s⁴. It was the time when sport became a form of popular culture. Today, the prevalence of doping is estimated at 3% to 5% in children and adolescents participating in sports and at 5% to 15% in adults⁵. Thus, doping represents a problem with multiple aspects that must be dealt with. The potential harmful effects on athletes and the depth of corruption of fair competition strongly advocate a vigorous campaign against doping.

The recent development of the World Anti-Doping Agency (WADA) is an endeavor of the international community to consolidate and coordinate efforts to minimize doping practice⁶. In this current anti-doping environment and in view of the Athens 2004 Olympic Games, the organizing committee “Athens 2004” in collaboration with the International Olympic Committee (IOC), the Medical Committee (MC) and WADA, will develop new anti-doping policies and will deliver programs and guidelines for doping control.

Doping represents a growing threat because of the serious damage to the health of athletes as the number of athletes who practice doping increases constantly. The aim of this review is to summarize the mode of action and the adverse effects of the most common doping agents and to emphasize the technical difficulties in the detection of the drugs or other substances in blood or urine.

NUTRITIONAL SUPPLEMENTS AND DOPING

The main substances prohibited by the International Olympic Committee (IOC) are listed in Table 1.

In the last decade, there has been an enormous increase in nutritional supplements and “sport foods” intake by athletes to help improve performance. Cur-

Table 1. Substances prohibited during and/or out of competition

Stimulants (e.g. amphetamine, ephedrine, bromantan)
Anabolic steroids
Peptide and glycoprotein hormones (e.g. GH, GHRH, ACTH, CRH, hCG, hrEPO)
Diuretics
Narcotics (e.g. morphine, methadone, pethidine)
Masking drugs (e.g. Probenecid, B-blockers)

rent data show that among dietary supplements, the most popular is creatine, a nutritional supplement considered as a safe ergogenic aid in adults⁷. However, as its safety has not been established, its use, especially in adolescents under the age of 18 years, should be discouraged⁸. Protein and carbohydrate supplementation provides modest benefits with no major known adverse effects⁹.

The problem of the widespread use of nutritional supplements by athletes, and especially by adolescents may intersect that of doping, as a large number of supplements may contain substances that are banned in sports¹⁰. Many supplements contain stimulants, such as ephedrine, that have been associated with high mortality. The removal of control over dietary supplements from the national drug administrations, initiated by the FDA in the last decade, has enabled the global distribution of nutritional supplements before their efficacy, safety and purity could be assessed¹¹. Therefore, physicians need to be prepared to address these issues on behalf of their athlete-patients as well as to educate trainers and parents about the safety of sports supplements and foods that may jeopardize not only sportsmen's health but also the very future of sports¹¹. Physicians can evaluate these products by examining available research data on adverse effects. Furthermore, the risk of an “inadvertent positive doping test”, through the use of sports supplements, exists in competitions governed by anti-doping rules and this should oblige the manufacturers to provide “doping safety standards” in special sports foods¹².

STIMULANTS

Psychomotor stimulants (cocaine, amphetamine and caffeine) and sympathomimetic amines (ephedrine, pseudoephedrine, phenylpropanolamine) are

widely used to ameliorate endurance, to increase concentration and competitiveness, to decrease sensitivity to pain and to reduce fatigue. They are used alone or in combination with other doping agents, mostly with AS (Figure 1). Caffeine and ephedrine taken together may improve performance during high-intensity aerobic activity lasting 20 min¹³. They are both easily detectable in urine samples. Athletes should be cautious with all decongestants or influenza remedies as the majority of them contain ephedrine. Short term high-intensity (100% V02-max) exercise might be improved by caffeine ingestion of 150-200 mg (2-3 cups of strong brewed coffee) through stimulation of the central nervous system and increase neuromuscular transmission. Caffeine is banned at 500-600 mg (5-6 cups). Amphetamines may improve power, endurance and speed, however, at the risk of arterial hypertension and tachycardia. Major sports where amphetamine abuse occurs are cycling, American football and ice-hockey¹⁴. Cocaine is regarded today as "the drug of greatest national health concern"¹⁵. The deaths of several US athletes in 1986 focused attention for the first time on the life-threatening cardiovascular consequences of cocaine abuse¹⁵. It is highly addictive and can cause cerebral and cardiovascular malfunction or even death¹⁴. It is often used in conjunction with AS.

The β_2 -agonist Clenbuterol has been used to increase muscle mass and to decrease fat mass since

the Olympic Games of 1992. Clenbuterol treatment may inhibit ephedrine to attenuate insulin-stimulated muscle glucose uptake. However, there are no studies of its efficacy in humans and, moreover, chronic clenbuterol administration negatively alters cardiac function¹⁶. Clenbuterol depletes potassium levels and the combination with diuretics may lead to cardiac conduction abnormalities.

ANABOLIC STEROIDS: THEIR ABUSE

The most easily available drugs for doping are the anabolic steroids (AS), derivatives of testosterone, that are used by athletes for their anabolic properties. The mechanisms of action include the stimulation of protein synthesis, antagonism of the catabolic effects of glucocorticoids, increase the capacity for more intensive training and through central nervous system effects increase motivation and decrease fatigue^{17,18}. However, they also possess virilizing effects that are more evident in children and women. Commonly used androgens are the orally administered mesterolone and testosterone undecanoate and the parenterally administered testosterone enanthate. The most widely used AS are metenolone enanthate and nadrolone decanoate

The use of AS began in the 1950s among weightlifters and spread rapidly through a variety of sports in both professionals and amateurs, men and women. By the time of the 1972 Olympics in Munich, nearly 70% of athletes in middle or short distance running and all the U.S weightlifters admitted to having taken AS¹⁹. The escalation of drug abuse resulted in the inclusion of the AS on the list of banned substances for all Olympic Games since 1976. However, it is difficult to collect epidemiological data due to the illicit nature of the drugs used.

AS are often combined with stimulants, supplements and/or growth factors (Figure 1). Over the last 15 years, combinations of at least two drugs have been frequent with constant increase of daily dose⁵. There have been long-standing discussions, mainly due to different dose regimens used to correct deficient states as compared to those used by athletes to enhance athletic performance, regarding the efficacy of the AS^{20,21}. Testosterone, the main gonadal steroid in males, has clear anabolic effects in developing boys or when used as replacement therapy. Its efficacy in

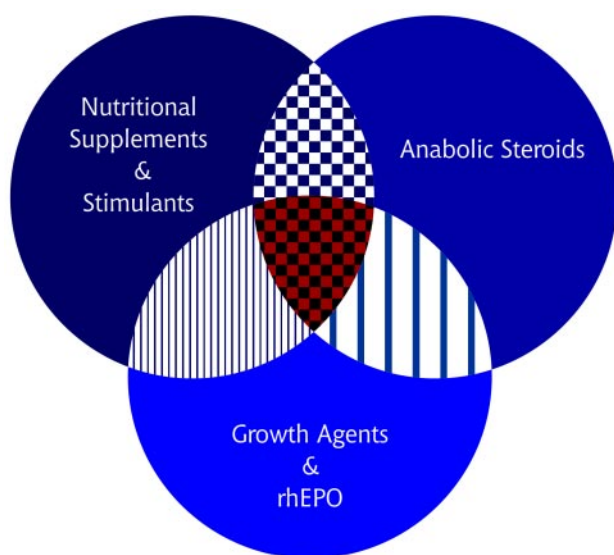


Figure 1.

eugonal men has been debated. However, recent data suggest that the use of suprapharmacologic doses can indeed be anabolic²¹.

The side effects of AS are dependent on dose and their metabolism. Misuse of AS is claimed to have serious side effects. The mortality in 62 male weightlifters placed 1st-5th in weight series 82.5-125 Kg in Finland was compared with the mortality of population controls²². The mortality during the 12-year follow-up was 12.9% for the weightlifters compared to 3.1% in the control population; thus, the risk of death among the weightlifters was 4.6 times higher²².

The 17-alkylated compounds can provoke impairment of hepatic function and dyslipidemia. There are no consistent changes reported for total cholesterol. The oral and the parenteral forms of 17-a-alkylated steroids, though not the parenteral forms of androgen esters, have been associated with a lowering effect on high density lipoprotein cholesterol (HDL-C), thereby increasing the chance of the development of coronary heart disease (CHD)^{23,24}. However, HDL-C fractions start increasing after cessation of AS use and tend to normalize in exercised men within 10 weeks²⁴.

In women users of AS, menstrual irregularities or cessation of menstruation are common. In men, a dose dependent decrease of LH and FSH is documented that may lead to reduced sperm count and abnormal sperm morphology²⁵. These findings are reversible in about 4 months after cessation of AS. In children and adolescents, AS use may lead to premature closure of epiphyses and therefore stunted growth.

The liver is a target tissue for androgens and, therefore, men develop hepatocellular carcinoma

more frequently than women. Both benign and malignant tumors have been reported in AS users²⁶⁻²⁸.

Generally, athletes taking AS for more prolonged periods are likely to suffer from more severe medical consequences²⁹. Those who do discontinue the AS treatment discover that the improvements made with the steroids disappear and have little to show for years of exhausting training beyond the psychological scars inherent in steroid use²⁹.

The abuse of AS may also cause psychiatric effects such as irritability, aggression, mood swings, diminished awareness of fatigue and depression³⁰.

The side effects of AS and related references are presented in Table 2.

It is not known whether the toxic side effects might be mitigated by intermittent use of the agents. Various agents have been used to mask the intake of AS and testosterone. The most common include epitestosterone, probenecid and HCG (Table 3).

GROWTH HORMONE

Growth hormone (GH) is released from the anterior pituitary in response to sleep, fasting, stress and to the administration of GHRH, GHRH-6 and other pharmacologic agents³¹. Doping with recombinant human GH (rhGH) has become an increasing problem in sports over the last 5 years and, more specifically, since the 1998 Tour de France, when several cyclists were found in possession of rhGH ampoules. Although its effectiveness is not undisputed, the abuse of rhGH will further increase because it is currently undetectable and because of its reputation as being very effective³². The use of rhGH seems not to be limited only to high-performance athletes as an anonymous survey showed that about 5% of male Ameri-

Table 2. Main adverse effects of AS

	Effects	References
Mortality	12.9% for the weightlifters compared to 3.1% in the control population	22
Cardiovascular system	Lowering effect on HDL, increased risk of developing CHD. Mainly 17-a-alkylated steroids	23, 24
Liver	Hepatomas and malignant tumors. Mainly by 17-a-alkylated steroids	20, 26, 27, 28
Skin	Acne, hypertrichosis in women	20
Chest	Gynecomastia in men, atrophied breasts in women	18
Reproduction	LH, FSH depression	25
Psychological effects	Depressed mood	30

Table 3. Drugs used to mask the intake of AS

Drugs	Function
Probenecid	Reduces excretion of AS into urine
Diuretics	Attain defined weight (furosemide)
Thyroid hormones	Accelerate metabolism
Anti-estrogens	Prevent gynecomastia
HCG	Alters testosterone/LH ratio and restores spermatogenesis
Epitestosterone	Reduces the testosterone/epitosterone ratio
Hypnotics	Promote sleep
Insulin	Promotes glucose uptake by tissues

can high-school students admitted to using rhGH as an anabolic agent³³. rhGH is very popular, due to its anabolic properties, among sprinters, weightlifters and body builders. However, it is known that GH results in voluminous but weak skeletal muscles. Additionally, prolonged rhGH abuse may lead to hypertension, diabetes and cardiomyopathy. Furthermore, there is no controlled study documenting any beneficial effect of supraphysiological rhGH doses on muscle strength. Thus, GH abuse is illicit not only for ethical reasons but also because it increases the risk of serious side-effects. Exogenous GH administration affects the biochemical parameters of bone formation and of bone resorption in a dose- and gender-dependent manner³⁴. After rhGH administration, serum bone-specific alkaline phosphatase, carboxy-terminal propeptide of type I procollagen (PICP), procollagen III N-terminal extension peptide (PIIIP) and carboxy-terminal cross-linked telopeptide of type I (ICTP) were elevated, and especially for PIIIP and ICTP the increase was much greater than after exercise³⁴. These findings together with those demonstrating a lipolytic effect, dependent on body weight, may have contributed to the popularity of hGH among athletes^{35,36}. However, there is no controlled study describing beneficial effects of hGH in healthy subjects. The discrepancies between scientific findings and subjective reports may be due to the varying doses used and to potential combinations with AS³⁶.

With acute administration of GH to healthy men, the serum concentration of IGFBP-2 decreases and the ratios of serum IGF-1/IGFBP-2 and IGFBP-3/IGFBP-2 increases³⁷. These considerations may be useful in the development of a test for detecting GH abuse in sport.

ERYTHROPOIETIN AND ARTIFICIAL OXYGEN CARRIERS

The production of red blood cells (RBC) is partly controlled by a glycoprotein, erythropoietin. Tissue hypoxia is the main stimulus for the synthesis of the hormone by the kidneys and the liver. In 1987, recombinant human erythropoietin (rEPO) became available and is being used with increasing frequency by athletes to ameliorate endurance and improve aerobic potential^{38,39}. However, its abuse as a performance enhancing drug by athletes is an unethical and dangerous procedure. Problems may arise with increasing viscosity of the blood. At hematocrit above 55%, the blood viscosity increases exponentially, which thus increases the risk of thrombosis and stroke⁴⁰. Decreased efficacy of rEPO has been observed in states of sideropenia, folic acid and vitamin B12 deficiency.

Tissue oxygenation and peripheral perfusion are pivotal factors to optimize performance in sport⁴¹. Maximal oxygen uptake is the major performance limiting factor in endurance sports. Blood doping and the misuse of rEPO have been tested in an attempt to improve maximal oxygen uptake⁴². Recently, a new class of substances has been introduced: the artificial oxygen carriers (AOC)⁴². The AOC, such as solutions based on recombinant hemoglobin and perfluorocarbon emulsions, may improve aerobic exercise capacity in animals and humans; however, both substances have lethal side effects including renal failure and systemic and pulmonary hypertension⁴².

METHODOLOGIES USED TO SCREEN FOR DOPING AGENTS

The presence of a drug in a biologic specimen can be used to document exposure. The detection of doping agents is a major challenge due both to the large number of compounds involved and to the sensitivity thresholds required in a small volume of urine¹⁷. The detection might also be complicated by the variability in the dosages and the structures of the androgens taken and their metabolites. The standard for drug testing is an immunoassay screen conducted on a urine sample. However, the most successful technique is a combination of gas-liquid chromatography (GG) and gas spectroscopy (GS) applied in urine specimens. The suspicious peaks are identified by GS and

their identity is established by mass spectroscopy¹⁸. These techniques were applied for the first time at the 1972 Olympic Games and since then have become very sophisticated¹⁹.

Mass spectrometry methods can be used to screen for xenobiotics at a certain sensitivity level. Isotopic mass spectrometry appears to provide means for resolving the problem of compounds with low molecular mass such as steroids^{43,44}.

Remarkable advances in sensitive analytic techniques have permitted the analysis of drugs in saliva or hair⁴⁵. Hair analysis by GC/MS might also be useful for the detection of anabolic steroids, beta-adrenergic compounds, ephedrine and other doping agents⁴⁶. It might be valuable to document the doping practice and demonstrate repetitive exposure to anabolic compounds as a complementary method to urinary analysis.

Recently, liquid chromatography/tandem mass spectrometry (LC/MS/MS), with a methanol-water gradient including 5mM ammonium acetate and 0.01% acetic acid, was found suitable to detect free anabolic steroid fractions in urine at low (ng/ml) levels⁴⁷.

Several methods for detection of GH abuse have been developed but they must be sufficiently validated before implementation⁴⁸. The heterogeneity of pituitary derived GH, which consists of a wide variety of GH isoforms, as well as its short half-life (about 20 min) are the main obstacles for a reliable detection of GH in organic fluids⁴⁹. rhGH consists almost exclusively of 22 kDa monomers. Administration of rhGH leads to a suppression of all isoforms except 22 kDa³⁶. Recently, an immunoassay approach has been developed using different monoclonal antibodies and based upon two specific immunoassays recognizing either the large panel of different GH isoforms or the 22kDa rhGH⁴⁹. An analysis of a serum sample by both assays could reveal the abundance of 22 kDa hGH in the serum. However, due to the low sensitivity of immunoassay, the changes of GH isoforms can be reliably detected only within 24-36 hours after the last exogenous administration³⁶.

Strenuous exercise may transiently increase all components of IGF-1 and GH pretreatment, further augmenting the exercise induced changes in ternary

complexes⁵⁰. Thus, serum total IGF-1, IGFBP-3 and ALS may be suitable markers of GH abuse but differences in the half-lives may decrease their sensitivity for detecting GH abuse⁵⁰. IGF-1 and IGFBP-3 are considered the most specific markers of rhGH administration. However, measurements of a single sample is not a sufficiently secure method to detect rhGH abuse, especially in low rhGH doses^{51,52}, due to genetic and inter-individual variations.

In regard to Hemoglobin enhancement by various unethical methods, it has been suggested that Hb be determined during training and the competition season to establish individual Hb mean values and range⁵³. The measurements of beta-globin mRNA by competitive RT-PCR of the hematocrit, the reticulocyte count and the soluble transferring receptor content in whole blood sample can detect rEPO abuse with a confidence interval of 99.9%⁵⁴.

In conclusion, doping by athletes is not only unethical; it is also very dangerous for the user, since it increases his/her chances for morbidity and mortality. The physician must be aware of the symptomatology involved and the expected adverse effects to facilitate identification of the user, especially among adolescents.

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