SUPPLEMENT

Central nervous system stimulants and sport practice

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Background and objectives: Central nervous system (CNS) stimulants may be used to reduce tiredness and increase alertness, competitiveness, and aggression. They are more likely to be used in competition but may be used during training to increase the intensity of the training session. There are several potential dangers involving their misuse in contact sports. This paper reviews the three main CNS stimulants, ephedrine, amfetamine, and cocaine, in relation to misuse in sport.

Methods: Description of the pharmacology, actions, and side effects of amfetamine, cocaine, and ephedrine.

Results: CNS stimulants have psychotropic effects that may be perceived to be ergogenic. Some are prescription drugs, such as Ephedra alkaloids, and there are issues regarding their appropriate therapeutic use. Recently attention has been given to their widespread use by athletes, despite the lack of evidence regarding any ergogenic or real performance benefit, and their potentially serious side effects. Recreational drugs, some of which are illegal (cocaine, amfetamines), are commonly used by athletes and cause potential ergolytic effects. Overall, these drugs are important for their frequent use and mention in anti-doping laboratories statistics and the media, and their potentially serious adverse effects.

Conclusions: Doping with CNS stimulants is a real public health problem and all sports authorities should participate in its prevention. Dissemination of information is essential to prevent doping in sport and to provide alternatives. Adequate training and education in this domain should be introduced.

Central nervous system (CNS) stimulants were originally used by athletes to improve performance on the day of competition. Although there was evidence that these drugs might be linked with sudden collapse or death, usually from cardiac or respiratory arrest, particularly during competition, the long term side effects of addiction and physiological damage to the body were regarded as minor or were not mentioned.[1–8] The class of stimulants includes psychomotor stimulants, sympathomimetics, and miscellaneous CNS stimulants—for example, caffeine, amfetamines, ephedrines, and cocaine (fig 1). These substances are either prohibited or monitored, previously by the International Olympic Committee (IOC) and now by the World Anti-Doping Agency (WADA), and are screened for daily by accredited laboratories (table 1).

Caffeine is the pharmacologically active substance found in tea, coffee, and cola. The amount of caffeine present varies according to the type of drink and the way it has been prepared. Caffeine may also be a constituent of some common medicines such as cold preparations and pain relief treatments, usually in quantities of less than 100 mg per dose. Caffeine produces mild CNS stimulation, similar to that of amfetamines, reducing fatigue and increasing concentration and alertness. Physiological effects include increased heart rate and output, metabolic rate, and urine production. High doses can cause anxiety, insomnia, and nervousness. In 2004 caffeine was removed from the list of prohibited substances and is now part of the monitoring programme.

Amfetamines are controlled substances under general drugs legislation, although they have been prescribed as appetite suppressants and for the treatment of narcolepsy. They are known to produce dependence, often in increasing doses. Athletes are likely to use amfetamines to sharpen reflexes and reduce tiredness. However, athletes have died as a result of amfetamine misuse, since the increase in blood pressure combined with increased physical activity and peripheral vasoconstriction makes it difficult for the body to cool down. If the body overheats, it dehydrates and blood circulation decreases, and the heart and other organs are unable to work normally.

The sympathomimetic drug ephedrine is used to treat symptoms of infection with the cold virus. It was originally prescribed as a bronchodilator for asthma, although it is now regarded as less suitable for this use since it has been linked with cardiac arrhythmia. Ephedrine is likely to be misused for its stimulant effect, but can also be ingested inadvertently because of its widespread availability in over-the-counter medicines.

Cocaine has been used as a medicine for many years. It was also one of the original ingredients of Coca-Cola until it was removed in 1903. Its therapeutic indication is as a local anaesthetic, although misuse is linked to its euphoric effects and feeling of decreased fatigue. Its potential for use as a recreational drug emphasises the lifestyle pressures faced by some athletes. In some disciplinary sports, such as sprinting, cocaine is likely to increase production of heat and lactic acid, which, coupled with vasoconstriction, could contribute to fatal cardiac arrest.

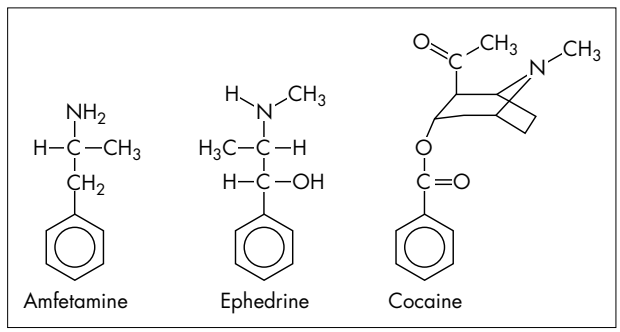

Figure 1 Chemical structure of amfetamine, ephedrine, and cocaine.

Table 1 Annual statistics for drug testing by IOC accredited laboratories

Year	Total A samples analysed	Number of positive samples with stimulants	% Positive samples with stimulants
2004*	169187	382	0.23
2003*	151210	516	0.35
2002†	131373	392	0.30
2001†	125701	352	0.28
2000†	117314	453	0.39
1999†	118243	532	0.45
1998†	105250	412	0.39
1997†	106561	356	0.33
1996†	96454	281	0.29
1995†	93938	310	0.33
1994†	93680	347	0.37
1993†	89166	331	0.37
1992†	87808	277	0.32
1991†	84088	221	0.26
1990†	71941	340	0.47
1989†	52371	508	0.97
1988*	47069	420	0.89

*Data from WADA, †data from IOC.

AMFETAMINE

Amfetamine[9–14] was synthesised in 1920 and was used to reduce fatigue and increase alertness during the second world war. Since then, many derivatives have been elaborated—for example, methamfetamine, dimethamfetamine, methylendioxyamfetamine (MDA), methylendioxymethamfetamine (MDMA, ''ecstasy''), and selegiline—and they are all forbidden in the practice of sport. Amfetamine was prescribed unsuccessfully as a nasal decongestant, antidepressant, and appetite suppressant, but soon appeared to be a powerful CNS stimulant. It acts primarily by enhancing the brain activity of noradrenaline and dopamine, intensifying psychological sensations of alertness, concentration, and self-confidence.

Metabolism

Amfetamine is readily absorbed, mainly from the small intestine, and the plasma concentration peaks one to two hours following administration. Absorption is usually complete in two and a half to four hours and is accelerated by food intake. The metabolism of amfetamine has been difficult to investigate because of the wide variation among species with regard to its metabolic effects. The principal amfetamine metabolites are p-hydroxy ephedrine and p-hydroxy amfetamine. Amfetamine is lost from the body by renal filtration. For detection of amfetamine use in sport, urine is analysed for the parent compound amfetamine. After a single dose of amfetamine, it has been shown that it can be detected in urine in the first urine void for at least 48 hours after the intake of the drug. The peak concentration in urine is strongly dependent on the individual, but occurs between 3 hours and 12 hours after the intake of the drug. Amfetamine excretion is enhanced by an acidic urine, and treatments that increase the acidity of urine enhance amfetamine loss—a reaction that is useful in the treatment of amfetamine overdose.

Actions and effects

The positive effects of amfetamine include an increase in physical energy, mental aptitude, talkativeness, restlessness, excitement, and good humour. Subjects taking amfetamine also report that they feel confident, efficient, ambitious, and that their food intake is reduced. Some negative effects of amfetamine (that can be dose dependent) are anxiety, indifference, slowness in reasoning, irresponsible behaviour, irritability, dry mouth, tremors, insomnia, and, following withdrawal, depression.

Tolerance develops rapidly to many of the effects of the amfetamines. Tolerance is said to be present when, over a period of time, increasing doses of a drug are required to maintain the same response. There is much evidence to show that amfetamines induce drug dependence and the amfetamine dependent person may become psychotic, aggressive, and antisocial. Withdrawal of amfetamines is associated with mental and physical depression.

The major side effects of amfetamine use include confusion, delirium, sweating, palpitations, dilation of the pupil, and rapid breathing, as well as hypertension, tachycardia, tremors, and muscle and join pain. Long term administration of amfetamine is associated with myocardial pathology and with growth retardation in adolescents. In most cases, the personality changes induced by chronic low doses of amfetamine are reversed gradually after the drug is stopped. High chronic doses may lead to a variety of persistent personality changes, paranoid delusions, and tactile hallucinations called ''amfetamine psychosis''.

Amfetamine in sport

The action of amfetamine on sporting performance was first investigated in 1959. It has since been concluded that amfetamines enhanced anaerobic performance while having little or no effect on aerobic performance. Amfetamines may enhance sports performance from a supplemental mental stimulant effect as well as the effects on physical power derived from all three human energy systems—the ATP-CP, lactic acid, and oxygen energy systems. Depending on the type of effect or effort the athlete has to do, the dosage might be important for the user. Aggressiveness seems to increase with high dosage, whereas alertness is stimulated by lower doses. To summarise, amfetamines may:

- improve reaction time when fatigued
- increase muscular strength and endurance
- increase acceleration
- raise lactic acid levels at maximal exercise
- increase aerobic endurance capacity
- stimulate metabolism by inducing a loss of body fat.

All amfetamines are banned by the WADA and IOC codes. Laboratory analysis is qualitative only, verifying presence of metabolites in urine. This is sufficient to demonstrate the presence of the substance in the urine and declare the case as an analytical adverse finding. The presence of amfetamine in urine can be described as a severe doping offence because amfetamines are no longer used therapeutically. Many countries prohibit its use because of the adverse effects. Amfetamines are part of the category S6 of the prohibited substances in competition.

Side effects of amfetamine in relation to sport

Side effects of amfetamine, besides headaches, sleeplessness and anxiety, are particularly important to athletes. Indeed, amfetamine use may carry significant health risks for the sportsperson as evidenced by several amfetamine-linked deaths in sport. Two of the major risks are amfetamine induced heatstroke and cardiac arrest, which have resulted in several fatalities among cyclists during arduous effort. Amfetamines obscure pain from injuries and have enabled athletes in some sports to continue to compete and thus exacerbated their injuries. The side effects of amfetamine with regard to behaviour also are important in sport. The euphoriant effects of amfetamine—taken to promote aggression and lower fatigue—has led in misjudgments and major fouls on the pitch.

COCAINE

Cocaine[15–19] is the most potent stimulant of natural origin. As opposed to amfetamines, which are pure synthetic compounds, cocaine is primarily obtained from Coca species and its notoriety belies the fact that the drug has been used as a stimulant for thousand of years. The Incas used to chew Coca leaves to fight against tiredness; cocaine was used in a number of patent medicines and even in soft drinks. In its pure form, cocaine is a white crystalline powder extracted from the leaves of the South American Coca plant. Pure cocaine was first used medicinally in the 1880s as a local anaesthetic in eye, nose, and throat surgery because of its ability to provide anaesthesia as well as to constrict blood vessels and limit bleeding. Many of its therapeutic applications are obsolete due to the development of safer drugs.

Cocaine can be snorted, smoked, or injected. When snorted, cocaine powder is inhaled through the nose and absorbed into the bloodstream through the nasal tissues. When injected, a needle is used to release the drug directly into the bloodstream. Smoking involves inhaling cocaine vapour or smoke into the lungs, from where absorption into the bloodstream is as rapid as by injection. Each of these methods of administration pose great risks to the user. Crack is cocaine that has been processed from cocaine hydrochloride to a free base for smoking. The most popular route of administration is snorting, which produces peak effect in 5–15 minutes, lasting for up to one hour. Inhalation of free-base cocaine produces peak effects in less than one minute and a short lived physiological effect measured in minutes.

Actions and effects

Cocaine is a strong CNS stimulant and is probably the most addictive agent known. Its recreational use is widespread, and it is highly addictive with its effect mediated through dopamine release. For ethical and practical reasons, most of the knowledge of the pharmacology of cocaine comes from animal studies or from addict reports. Classic physical effects of cocaine use include constricted blood vessels, dilated pupils and increased temperature, heart rate and blood pressure. It also increases motor activity and talkativeness and is a strong inducer of euphoria. The duration of cocaine's immediate euphoric effects (hyperstimulation, reduced fatigue, and mental clarity) depends on the route of administration. The faster the absorption, the more intense are the effects and the shorter the duration of action. The effects from snorting may last 15–30 minutes whereas the effects from smoking may last 5–10 minutes. Increased use can reduce the period of time a user feels high and increases the risk of addiction.

Cocaine users usually feel an initial ''rush'' or sense of wellbeing, of having more energy and being more alert. This effect quickly wears off, often leaving the user feeling more ''down'' or depressed than before. This down feeling leads the addict to use more cocaine, sometimes just to feel ''normal''. Over a period of time, the amount of cocaine needed and the frequency of use to achieve a ''high'' have to be increased.

Cocaine is more addictive than amfetamine and the increasingly higher doses used by addicts may lead to a state of irritability, restlessness, anxiety, and paranoia. Other complications associated with cocaine use include disturbances in hearth rhythm and heart attacks, chest pain and respiratory failure, strokes, seizures and headaches, and gastrointestinal complications such as abdominal pain and nausea. Cocaine misuse is strongly associated with cerebrovascular accidents arising either from rupture or spasm of cerebral blood vessels. Different means of taking cocaine can produce different adverse effects. Regular snorting, for example, can lead to loss of sense of smell, nosebleeds, problems with swallowing, hoarseness, and a chronically runny nose. Ingesting cocaine can cause severe bowel gangrene due to reduced blood flow. People who inject cocaine can experience severe allergic reactions and, as with any injecting drug user, are at increased risk for contracting human immunodeficiency virus (HIV) infection and other bloodborne diseases.

Cocaine in sport

Despite the popular myth, cocaine does not really enhance performance, whether in the job, in sports, at school, or during sex. On the contrary, long term use can lead to loss of concentration, irritability, loss of memory, paranoia, loss of energy, anxiety, and a loss of interest in sex. In particular, several studies have shown that cocaine has no beneficial effect on running times and reduces endurance performance. Furthermore, at all doses, cocaine significantly increases glycogen degradation while increasing plasma lactate concentration without producing consistent changes in plasma catecholamine levels. The controlling effect of cocaine on an addict's life can lead to exclusion of all other facets of life. Nevertheless, despite these apparently detrimental effects, cocaine continues to be misused in sport. It may be that cocaine only affects activities of short duration requiring a burst of high intensity energy output. It is possible that the central nervous stimulatory effect may be more important than its action on peripheral metabolism. It has been suggested that athletes are drawn to cocaine because of the effects of heightened arousal and increased alertness, achieved principally at low doses.

Federal regulations for cocaine were introduced in December 1914. This act banned non-medical use of cocaine, prohibited its importation and selling. Cocaine can currently be administered by a doctor for legitimate medical use, such as for local anaesthetic use for some eye, ear, and throat surgeries. Cocaine is banned by both WADA and IOC, including its use as a local anaesthetic. Like amfetamines, it comes under category S6 of the prohibited substances in competition. The presence of cocaine and/or its metabolites (benzoylecgonine and methylecgonine) in urine can be described as severe doping offence.

Side effects of cocaine in relation to sport

A number of dramatic fatalities associated with coronary occlusion have occurred in athletes misusing cocaine, usually those who have been exercising intensely following drug administration. Many sportspeople who misuse cocaine complain of negative central effects such as perceptual misjudgments and time disorientation that sometime reduce their athletic performance. Furthermore, cocaine addicts frequently turn to other drugs to relieve the down feeling when more cocaine is not available. When used together, these drugs and cocaine can prove even more deadly than when used alone. Some fatalities have also occurred when cocaine misuse has been mixed with alcohol or anabolic steroids. The joint misuse of alcohol and cocaine is extremely cardiotoxic. These practices increase the risk of sudden death by cardiac arrest or seizures followed by respiratory arrest.

EPHEDRINES

Ephedra alkaloids,[20–28] which are popular components of many nutritional supplements, are naturally occurring CNS stimulants obtained from several Ephedra species. Purified forms of these substances include ephedrine, pseudoephedrine, norephedrine, methylephedrine, norpseudoephedrine and methylpseudoephedrine. Phenylpropanolamine is a synthetic compound functionally similar to the ephedra alkaloids in effect and use. Ephedrine, which is now also produced by chemical synthesis, is closely related in structure to metamfetamine, although its CNS actions are much less

potent but longer acting than those of the amfetamines. Its peripheral stimulant actions are similar to, but less powerful than, those of adrenaline (epinephrine), a hormone produced in the body by the adrenal glands.

Actions and effects

Ephedrine is the most potent thermogenic of the Ephedra alkaloids. It is a mixed sympathomimetic agent which acts as a CNS stimulant by enhancing the release of noradrenaline from sympathetic neurones and stimulating α and β receptors. Ephedrine not only stimulates the heart rate and thereby increases cardiac output, but also causes peripheral constriction, resulting in an increase in peripheral resistance—which can lead to a sustained rise in blood pressure. Ephedrine has moderately potent bronchial smooth muscle relaxant properties, and is used as a decongestant and for temporary relief of shortness of breath caused by asthma.

Historically, Ephedra alkaloids have been used for both asthma and allergies in China for more than 5000 years. Currently, it is found in various pharmaceuticals, mainly as a decongestant, and in numerous nutritional and dietary supplements as an energy stimulant and anorexic agent. Pseudoephedrine can be found in many prescription and over-the-counter preparations for respiratory infections or allergies (mostly for the treatment of congestion). Until its recent voluntary removal from the market because of reports of increased risk for stroke in women, phenylpropanolamine was also used similarly to pseudoephedrine and in over-the-counter diet pills.

Ephedrine is excreted in the urine largely unchanged and the usual elimination half-life is three to six hours which can be prolonged with increased urine pH.

The common side effects of ephedrine are qualitatively similar to those produced by amfetamines but are generally milder: headache, dizziness, irritability, anxiety, tremor, and psychosis. Higher doses (overdose) can cause restlessness and anxiety, dizziness, insomnia, tremor, rapid pulse, sweating, respiratory difficulties, confusion, hallucinations, delirium, and convulsions. The most dangerous symptoms of overdose are abnormally high blood pressure and rapid, irregular heartbeat. A dose of ephedrine only two or three times the therapeutic maximum can cause a significant increase in blood pressure. Finally, a number of instances of psychosis, clinically similar to amfetamine psychosis, have resulted from chronic high-dose misuse.

There are serious doubts concerning the safety of food supplements containing ephedra alkaloids. Because supplements are not considered therapeutic, they are not held to the same level of rigor in claiming efficacy and safety as that required of prescribed and over-the-counter medicines. Since the 1994 deregulation, an increased number of reports of adverse events, including hypertension, arrhythmia, myocardial infarction, seizure, cerebrovascular accidents and death, has prompted the US Food and Drug Administration to recommend a limit on the use of ephedra alkaloids. Furthermore, joint use of ephedrine and caffeine can augment adverse cardiovascular and CNS effects.

Ephedrine in sport

With their stimulant properties and sympathomimetic actions, ephedra alkaloids have been perceived as products that can potentially be used to enhance athletic performance and lending unfair advantages to athletes, even if used in supplement forms. Research has shown that the isolated use of ephedrine, pseudoephedrine and phenylpropanolamine alone at usual dosages has an inconsistent, and probably insignificant, ergogenic benefit for power, endurance, strength, or speed. Other studies looking at the use of ephedrine combined with vitamins, minerals, or caffeine have supported potential ergogenic effects. Indeed, many athletes use food supplements containing ephedra alkaloids because of perceived benefits of increased energy, decreased time to exhaustion and potential thermogenic properties with increased metabolism, increased fat loss, and improved muscle strength. In particular, a series of studies evaluated the effects of ephedrine in combination with caffeine showing an increased time to exhaustion and decreased rating of perceived exhaustion on cycle ergometry compared with either drug alone or placebo.

The medical use of ephedrine is tolerated by WADA and IOC at therapeutic levels. Nevertheless, urine concentrations of greater than 10 μg/ml are considered positive. Ephedrine is a category S6 prohibited substance.

Side effects of ephedrine in relation to sport

The recent highly publicised tragedies have prompted various athletic associations to focus on further evaluations of the use of these substances and on trying to educate athletes about potential health risks associated with their use. Continued evaluation of the use of these substances is necessary, as is continued education of athletes, parents, coaches, and trainers regarding the health risks associated with ephedrine alkaloids and corresponding supplements.

CONCLUSION

The actual ergogenic benefits of amfetamines, cocaine, and ephedrines are unclear, but all are banned or monitored to varying degrees by different sporting federations and associations in relation with their real side effects in sport practice. This discrepancy between actual benefit and banned status highlights the difficulty sport physicians have in advising athletes, parents, coaches, and the sporting community about the proper approach to monitoring, education, and testing for these drugs. Together, they should take action in the areas of education, scientific research, and social and health measures to protect athletes, harmonise standards and coordinate the legislation in relation to doping. In particular, harmonising the regulations of sports has become a major international objective, and expectations are high that the

What is already known on this topic

CNS stimulants are used in sport to reduce tiredness and to increase alertness, competitiveness, and aggression. Stimulants are more likely to be used on the day of a competition; however, they may be used in training, to allow the intensity of the training session to be increased. Since stimulants could increase an athlete's aggression towards other competitors or officials, there are potential dangers involved in their misuse in contact sports.

What this study adds

This review outlines some aspects of doping with CNS stimulants such as amfetamine, cocaine and ephedrine. This appears to be, outside its use in performance enhancement, a real public health problem and its prevention is an absolute necessity in sports practice. As statistics show constant use of these substances since many years, the introduction of stimulant detection out of competition is perhaps a reasonable solution. Moreover, the increasing number of cocaine cases is possibly more an image of the social use of this substance.

new World Anti-Doping Agency might lead to such resolution.

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