Erythropoietin – Blood Doping
Introduction to Erythropoiesis

Erythropoiesis is part of a large process of haematopoiesis that involves the production of mature cells found in the blood and lymphoid organs. Haematopoiesis is continuously required because of normal turnover in cell populations of blood and lymphoid organs. In the normal adult human, the daily turnover of erythrocytes exceeds 1011 cells. In periods of increased erythrocyte loss due to haemolysis or haemorrhage, the production of erythrocytes increases rapidly and markedly. However, an overproduction of erythrocytes does not occur even after the most severe loss of erythrocytes.

In haematopoiesis, a few rare haematopoietic stem cells in the bone marrow proliferate and differentiate to give rise to all the cellular components of the blood and the lymphoid system. During this process, an individual haematopoietic cell undergoes an apparent random process called commitment. When a cell undergoes commitment, its proliferation becomes limited and its potential to develop into multiple types of mature cells is restricted. Thus, these haematopoietic cells are referred to as committed, lineage-specific progenitor cells.

The major stages of differentiation in mammalian erythropoiesis are:

• The most immature stage of committed erythroid progenitors is the burst-forming unit-erythroid (BFU-E).
• The next major stage of erythroid progenitor cell development is the colony-forming unit-erythroid (CFU-E).
• A continuum of erythroid progenitor stages exists between the BFU-E and CFU-E, with decreasing proliferative potential as the progenitors approach the CFU-E stage.
• The descendant cells of the CFU-E are termed erythroid precursor cells.
• The erythroid precursors are proerythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts and orthochromatric erythroblasts. The orthochromatric erythroblasts do not divide but they enucleate, forming the nascent erythrocyte called the reticulocyte.

Production of Erythropoietin

EPO is a 30,400 molecular weight (MW) glycoprotein hormone produced mainly in the kidney, in the liver (<10%) and, in very small quantities, in the brain. The physiological stimulus for EPO production is tissue hypoxia, which, in the vast majority of instances, is directly related to the number of circulating erythrocytes.

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Thus, EPO and erythropoiesis are part of a negative feedback cycle that keeps tissue oxygen delivery within a narrow range by controlling the number of erythrocytes circulating in the blood. In a normal individual, any loss of erythrocytes, such as by bleeding or haemolysis, decreases delivery of oxygen to the tissues. When this tissue hypoxia is sensed by cells capable of producing EPO in the kidney and liver, they produce and secrete EPO into the plasma. EPO is carried to the bone marrow, where it binds to specific cell-surface receptors on its target cells – the CFU-E, pro-erythroblasts and basophilic erythroblasts. The binding of EPO by these cells increases their ability to survive and reach the reticulocyte stage and thereby contribute to the population of circulating erythrocytes. The increased numbers of circulating erythrocytes in turn deliver more oxygen to the tissues. This increased oxygen delivery is sensed by the EPO-producing cells, which then reduce EPO production so that the normal steady-state number of erythrocytes is maintained.

The response of the kidneys to hypoxia has been shown to be exponential. In individuals with a normal capacity to produce EPO, a linear decline in haematocrit is accompanied by an exponential increase in plasma EPO levels. This exponential increase is not based on the release of stored, pre-formed EPO. Rather, the hypoxia is sensed by an intracellular molecule that interacts with an enhancer element of the EPO gene that induces transcription of the gene. The increase in EPO production in the hypoxic kidney is achieved by recruitment of more cells to produce EPO. The EPO-producing cells of the kidney are a minor subset of cortical interstitial cells. Only a few scattered cells produce EPO under normal conditions. When a threshold level of hypoxia is achieved, those cells capable of producing EPO do so at a maximal rate. The greater the areas of renal cortex in which the hypoxia threshold has been met, the greater the number of cells that produce EPO.

Mechanism of Erythropoietin Action

In bone marrow, EPO binds to receptors displayed on the cell surface of CFU-E, proerythroblasts and basophilic erythroblasts. The mature EPO receptor is an approximately 72,000 MW, transmembrane glycoprotein that is a member of a much larger family of receptors of cytokines and haematopoietic growth factors. The cellular effect of EPO binding to its receptor has been shown to be the prevention of programmed cell death (apoptosis). In multiple systems of erythropoiesis, EPO has been shown to be a survival factor for the erythroid cells in the later stages of differentiation from the CFU-E through basophilic erythroblasts. Although an effect of EPO on mitosis has been reported for BFU-E and an EPO-dependent cell line, EPO is required only for the stages of CFU-E and later, and that apoptosis appears to result when EPO signaling cannot occur.

Detecting rhEPO Abuse In Sport

The availability of recombinant EPO (rhEPO) in 1987 in Europe made it clear that this ergogenic hormone would be used illicitly in endurance sports. Therefore,
the IOC Medical Commission decided to ban this drug in 1990 even though all forms of blood doping were already officially banned since 1984. Two philosophies were developed for the detection of rhEPO abuse in sports. The first was based on the detection of indirect blood markers and the second was based on the direct detection of rhEPO in urine. The promotion of secondary blood markers was based mainly on the fact that they could be used to detect rhEPO injections performed a long time ago (more than a week) and also that they could be used to detect all kinds of erythropoietic stimulators such as erythropoietin α, β, γ, darbepoitin and mimetic peptides. Furthermore, secondary blood markers could eventually be used to detect athletes who ceased using rhEPO or other erythropoietic stimulators. In the meantime, scientists were working on the direct detection of rhEPO in blood or urine. This latter detecting method had the advantage of identifying the drug itself (or metabolites), but had the disadvantage of being expensive, of low sensitivity and delicate to perform.

**Indirect Methods**

With the introduction of sophisticated haematological analysers in 1993, some scientists proposed a model implicating the analysis of the percentage of red blood cells having a mean corpuscular haemoglobin concentration below 28 pg (MCH) and a mean corpuscular volume above 128 fl (MCV). These red blood cells are called macrocytic hypochromic erythrocytes. This test had the advantage of being fast and cheap (as long as the laboratory was equipped with this special analyser) and was very selective. Unfortunately, the test was limited by a relatively poor sensitivity, as 50% of the rhEPO samples were not detected.

Another indirect test was developed in 1996 for the detection of rhEPO abuse, based on the determination of the sTFR/total protein. The lack of sensitivity of some of the secondary blood markers as well as the lack of specificity of some others encouraged scientists to put them together in order to obtain a multiple-marker mathematical model to distinguish rhEPO abusers from healthy sportmen. Following a double blind study with regular rhEPO injections (continuous treatment), the Australian Institute of Sport together with the Australian Sports Drug Testing Laboratory designed an anti-doping test using multiple secondary blood markers such as the haematocrit level, the reticulocyte haematocrit, serum sTFR and EPO concentrations and the percentage of macrocytic cells. Different mathematical models allowing the identification of sportmen under rhEPO treatment (ON-model) and those who took rhEPO in recent days (OFF-model) were developed.

In August 2000, the IOC Medical Commission approved the ON-model for use during the Sydney 2000 Olympic Games. As the direct method capable of discriminating endogenous EPO from rhEPO was published in spring 2000, the ON-model was only used as a screening test to determine which urine samples had to be collected to perform the urinary test.

At the same time as the study was performed in Australia, the LAD (Laboratoire Suisse d’Analyse du Dopage) conducted a very similar controlled randomised double blind trial, with the exception that iron supplementation was much more important and delicate to perform. Therefore, the behaviour of secondary blood markers was different during continuous treatment. In contrast to the Australian study, the Swiss demonstrated that some of the secondary blood markers (haematocrit, haemoglobin and reticulocyte count) could be used as part of a screening test, but in no case could be used for anti-doping purposes.

**Direct Methods**

Endogenous EPO and rhEPO are slightly different and these differences come from glycosylation of the EPO, which takes place in Chinese hamster ovary (CHO) cells rather than in human cells. Indeed, the post-translational modifications are species- and tissue-depandant and also depend on the cell culture conditions. Therefore, it is possible to separate the endogenous from the exogenous EPO isoforms thanks to the different charges of the different sugar structures. The technique developed by Wide (2002) allowed the separation of the different isoforms thanks to the differences of charges on the different structures of sugars. This technique was very reliable in urine and in blood as long as the biological samples were collected within 24 hours after the last rhEPO injection. Unfortunately, once the rhEPO treatment was ceased for more than three days, less than 50% of the treated subjects could be declared positive.

A few months before the Summer Olympic Games in Sydney, the French anti-doping laboratory in Paris published in Nature a novel test based on the isoelectric focusing pattern and a double blotting protocol. The exogenous isoforms of rhEPO are less acidic than the endogenous EPO, making it possible to find the convenient protocol to separate them using the isoelectric focusing method. This test was designed to separate α, β and to rhEPO (see Figure 1).

**Targeting rhEPO Abusers**

The LAD and selected federations made the decision to launch the blood screening test based on the determination of the haemocrit, the haemoglobin and the reticulocyte count. It was introduced during the 2001 cycling season at the Tour des Flandres. The blood test quickly demonstrated its ability to detect rhEPO abusers. Since then, more sport federations have decided to introduce the screening test set up in Lausanne. With time, this test has shown to be even more efficient in the follow-up of athletes (blood profile). Variations above normal were excellent indicators of blood manipulation.
Abnormal Blood Profiles

For approximately two years, abnormal blood profiles have been noticed without any traces of rhEPO in urines. This meant that athletes were either doping with undetectable compounds or had returned to “ancient” doping techniques such as blood transfusion. In the 1970s, blood transfusion was a common practice for enhancing oxygen transport from the increase of red blood cell mass. This method of doping virtually disappeared with the arrival of rhEPO on the market at the end of the 1980s because the use of the hormone is much easier (to store and to use) and cheaper. The launching of the direct detection test of rhEPO in urine samples in 2000 had an unwanted side-effect: a return to blood transfusion. The regular follow-up of some blood parameters such as haematocrit, haemoglobin and reticulocyte count suddenly showed that some athletes who demonstrated abnormal blood parameters although rhEPO could not be detected in urine. This clearly indicated a return to blood transfusion practices. With the possibility of analysing specific red blood cell membrane proteins defining the different blood groups and sub groups, the LAD decided to perform anti-doping tests in blood for the first time (summer 2004). The specific labeling of some red blood cell membrane proteins in combination with flow cytometry detection proved that abnormal blood profiles were due to homologous blood transfusion. Federations that have introduced blood testing now have a powerful tool to follow all athletes potentially abusing rhEPO or blood transfusion. Therefore, they need to focus their anti-doping tests on those demonstrating abnormal blood profiles.

Conclusion

It is likely that all cases of blood doping and rh-EPO abuse will be identified in the near future. The necessity to take blood samples in order to screen and test for this type of doping habits has become obvious for sports authorities. In this field, there is still a need for more research and coordination with anti-doping panels to target the use of blood manipulation better. Haematological follow-up of the sportsmen is certainly one of the solutions for this targeting. Besides, new biochemical investigations should allow the scientists to improve the tools for direct detection of this sort of doping.

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Human Growth Hormone

Introduction

Growth hormone (GH) is a naturally occurring peptide hormone secreted by the pituitary gland. Even though the hormone in the body is rather heterogeneous, the major component is made of 191 amino acids, stabilised by two disulfide bonds and reaching the molecular weight of 22 KDa. Previously, the only source of human GH (hGH) was human cadavers, but contamination by Kreutzfeldt-Jacobs disease made this form of treatment obsolete. Since the late 1980s, recombinant human GH (rhGH) has been developed through genetic engineering and is used clinically with good results in the treatment of hGH-deficient patients to allow bone growth and impact on the patient’s final stature. This form of hGH has an identical sequence to the naturally occurring 22 KDa hormone. Its abuse was suspected in sport because of its anabolic properties. It was claimed by athletes and bodybuilders that hGH increased lean body mass and decreased fat mass.

The use of hGH in sport today is not only based on its anabolic properties, but on its effect on the metabolism of carbohydrate and fat. Recombinant hGH has been found in swimming and also during the Tour de France in 1998. International federations and the IOC have had hGH on the list of forbidden compounds since 1989, when it became obvious that the development of biotechnology products based on the recombination of DNA made it much easier to obtain the product on the regular and black markets. It is on of the 2006 FIFA list of prohibited substances in class S2 of hormones and related substances. EPO (erythropoietin) and ACTH (corticotropin) as well as IGF-1 and insulin belong to the same category of peptide hormones.

Pharmaceutical Action of hGH

Human GH is secreted by somatotrope cells in the anterior pituitary. Its secretion is pulsatile and is regulated by two hypothalamic peptides, growth hormone releasing hormone (GHRH) that stimulates hGH secretion and somatostatin, which inhibits hGH secretion by back-regulation. hGH applies its biological effects on target cells by binding to specific receptors present throughout the whole body.

Secretion by women is slightly higher than by men, with the highest levels observed at puberty. There is a decrease in hGH secretion with age of around 14% per decade. Moreover, hGH secretion varies with normal physiological and pathological conditions. hGH levels are higher during slow-wave sleep and are increased by exercise, stress, fever and fasting with some amino acids (leucine and arginine). Some specific drugs such as clonidine, L-dopa and GHB (gamma-hydroxybutyrate) increase its secretion, as androgens and estrogens do.

Therapeutic Use of hGH

hGH is prescribed for both childhood and adulthood hGH deficiency and for children with Turner’s Syndrome. High doses of hGH are used for relief from excessive burns or other thermal injuries. hGH-deficient children have been treated since the end of the 1950’s with hGH extracted from cadaveric pituitaries. Recently, due to the better availability of recombinant growth hormone, hGH deficiency in adults has been recognised as a clinical syndrome and studied through clinical

The effectiveness of rhGH in the improvement of sport performance is still under debate among users.
The major studies of hGH therapy in hGH-deficient adults have demonstrated that hGH treatment for a period of 4 to 6 months shows favourable effects on body composition, exercise aptitude, renal and cardiac functions, and in general, an improvement of the quality of life. In long-term experiments, an increase in bone mass and persistence of the positive effects of hGH therapy has been observed.

The positive effects on body composition are essentially due to the anabolic, lipolytic and anti-natriuretic properties. An increase in the body cell mass (muscles) and total body water will be observed. The hGH dose in adults is generally individualised, but the typical dose is 1-2 IU/day applied subcutaneously every evening. With therapeutic doses, no adverse side-effects have been observed.

hGH as Doping Agent

Growth hormone has been considered as an ergogenic drug since the late 1980s. Since that time, official and non-official sources report that abuse in sport has increased steadily. The popularity of the product is based on the popular knowledge that it is efficient, hard to detect and without major side-effects if well dosed.

The frequency of use and the dosage are hard to evaluate, but underground information suggests that the athletes abusing hGH are taking 10-25 IU/day 3 to 4 times a week to increase their lean body mass. We tend to think that mean doses are about 4 IU/day in combination with other doping agents such as anabolic steroids in power sports or EPO in endurance sport.

The treatment is often applied in cycles of 4 to 6 weeks as is the case for anabolic steroids in bodybuilding. In endurance sport, very little is known on the optimum utilisation of hGH doping in combination with other products. It is very individual and empirically based.

The effectiveness of hGH in the improvement of sport performance is still under debate among users. The results of controlled studies are generally not in agreement with subjective underground reports by abusers, it is difficult to draw any definite conclusions regarding the effects of excessive hGH administration on skeletal muscle function. It must be stressed that the habits of hGH users in sport are designed to reach purposes other than just an increase in their muscle mass. The doses involved are certainly specific to the discipline, its training model and to the regime of other ergogenic substances used concurrently.

Adverse Effects of hGH

The long-term risks due to utilisation of hGH are not well known since epidemiological data regarding that type of treatment in healthy sportsmen are unavailable. Acromegaly, a pathological increase in endogenous production, is often cited as one of the major risks associated with excessive use of hGH. The major symptoms are swelling of the hands and feet, coarsened facial appearance, dentition problems, arthralgias, fluid retention and excessive sweating. Acromegalic patients have an increased risk for diabetes mellitus and hypertension leading to premature mortality from cardiovascular diseases. It can be argued that long-term hGH doping with elevated dosage will probably result in abusers suffering fluid retention symptoms and the increased risk of development of diabetes mellitus and hypertension. There is also a risk of cardiomyopathy, osteoporosis, menstrual irregularities and impotence. Some of these side-effects are reversible after withdrawal of the drug. Furthermore, hGH abuse can disturb the lipid profile with decreased HDL-cholesterol.

Since hGH is administered by injection, if syringes are non-sterile or contaminated, there is a risk of cross infections such as HIV/AIDS and hepatitis. Even though cadaveric hGH is now rare in the black-market, its use is associated with a high risk of developing Creutzfeldt-Jacob disease, which is characterised by slowly progressive dementia.

Detection Of hGH Doping

Until the Olympic Games of Athens 2004, hGH doping was considered undetectable. Growth hormone is a peptide with a very short half-life in blood and low concentration in urine. The peptide nature of the substance forces analysts to investigate other methods than that used in the classical analyses for anabolic steroids or stimulants with relatively low molecular weight. The amino acid sequence of the recombinant molecule is identical to the major 22 KDa isoform, which is secreted by the pituitary gland. There is no possibility to use a post-transcription modification of the molecule to find the difference between the recombinant and the natural form.

Secrecion of hGH by the pituitary gland is pulsatile, leading to highly fluctuating levels in the circulation. Moreover, hGH is considered as a stress hormone regulated by factors such as sleep, nutritional status, exercise and emotion. Thus, the secretion of hGH is highly variable, both intra- and inter-individually.

Quantifying the hormone itself is not sufficient to detect exogenous recombinant growth hormone. More stable serum parameters implied in the biological cascade produced by hGH secretion, or a doping application, may be the route of successful detection of hGH. The growth factor (IGF-1), or some of its transport proteins (IGFBP-3), have been proposed as possible candidates for indirect detection of hGH doping. But the inter-individual variability is quite high and makes it hard to precisely define a quantitative cut-off level.

Urine Strategy

Most of the anti-doping samples are taken from urine collected out of competition or after effort. Because of its convenient availability and the relatively unlimited volume, some attempts to use urine for peptide detection have been conducted. For example, urine could be used for successful detection of EPO because of the glycosylated form of this hormone. However, the only way to detect hGH in urine is to apply an extremely sensitive immuno-test to quantify the total amount of the hormone in urine. The average urine concentration of hGH is between 100 to 1,000 times less than in blood, but the idea was to develop a screening test for out-of-competition testing in order to benefit from a relatively longer detection time window. The limitations of that test have been clearly demonstrated because of the large influence of renal excretion process on the concentration measured in urine. The lack of discrimination and specificity of the answer made the urinary test less promising than a blood test.

The Indirect and Direct Approaches in Blood

Two main strategies are currently being followed to detect hGH doping using blood.

Indirect Approach

The increasing knowledge about the naturally occurring variability of serum hGH-dependent parameters (i.e. growth factor IGF-1, different IGF binding proteins (IGFBPs), or several makers of the bone turnover) may, individually or in combination, provide a database for establishing normal ranges for the concentration of these parameters. This may lead to an establishment of cut-off levels and describe so-called abnormal values outside of the normal constellation of parameters.

This approach, proposed in the mid-1990s, was investigated by an international panel of endocrinologists, but did not lead to a solution for...
HGH-doping detection. One of the elements from all these investigations is that the indirect approach can be used for screening and targeting purposes. HGH, IGF-1 and IGFBP-3 in the HGH biological cascade as well as selected peptides involved in bone metabolism (for example the N-terminal peptide from pro-collagen named PIIIP) or osteocalcin can play a role in the definition of individual normal ranges in athletes. Based on these observations, samples for sensitive and specific characterisation of doping offences can be collected in order to apply a direct detection of HGH abuse.

Direct Approach

The Strasburger-Bidlingmaier group in Munich has developed a so-called direct method for the detection of HGH doping. Two specific immunoassays have been developed in order to quantify several types of HGH isoforms. Recombinant HGH is exclusively represented by the native 22 KDa form, whereas the circulating HGH in the human blood is present in several forms (Table 1). When the recombinant form is injected into the body, this will increase, for a period of time, the ratio of the 22 KDa in comparison to all other circulating forms. Moreover, with long-term treatment, the classical back-regulation on the endogenous secretion of natural HGH will occur and the proportion will favour the major 22 KDa sequence.

The proposed test was used during the Olympics in Athens. In order to fulfill the requirements of the World Anti-Doping Code and the standards for laboratories, two double tests were applied to serum samples: the first test quantified specifically the 22 KDa and the second test was a comprehensive assay measuring all forms present in the serum (Figure 1). The ratio was established and a cut-off defined to differentiate the normal subjects (negative samples) from those having a significant higher proportion of 22KDa HGH (positive samples). A second double sample test was used for confirmation purposes. The detection window for these tests is between 24 to 36 hours after the last injection, depending on the dosage used. It is supposed that HGH-doping, to be efficient, needs multiple injection treatments. It has also been shown that the direct test is not influenced by environmental parameters such as exercise or stress. If applied in out-of-competition tests, direct tests should be a deterrent.

References

Therapeutic Use Exemption

Football players who suffer from acute or chronic disease or physical symptoms and sign following injury may need a disease- or injury-specific medication for treatment which might be on the prohibited list.

According to the clinical situation, a Therapeutic Use Exemption (TUE) may be granted to a player, permitting the use of a prohibited substance or method contained in the prohibited list. An exemption will be granted only in strict accordance with the following criteria (FIFA Doping Control Regulations 2006; World Anti-Doping Code (WADC)):

• The player shall submit an application for TUE no less than 21 days before participating in an event.

• The player would experience a significant impairment to health if the prohibited substance or method were to be withheld in the course of treating an acute or chronic medical condition.

• The therapeutic use of the prohibited substance or method would produce no additional enhancement to health if the prohibited substance or method were to be withheld in the course of treating an acute or chronic medical condition.

• There is no reasonable therapeutic alternative to the use of the otherwise prohibited substance or method.

• The necessity for the otherwise prohibited substance or method cannot be a consequence, wholly or in part, of prior non-therapeutic use of any substance or method contained in the prohibited list.

• The TUE will be cancelled by the granting body, if:
  a. The player does not promptly comply with any requirements or conditions imposed by the FIFA Doping Control Sub-Committee granting the exemption.
  b. The term for which the TUE was granted has expired.
  c. The player is advised that the TUE has been withdrawn by the FIFA Doping Control Sub-Committee.

• An application for a TUE will not be considered for retroactive approval except in cases where:
  a. Emergency treatment or treatment of an acute medical condition was necessary, or
  b. Due to exceptional circumstances, there was insufficient time or opportunity for an applicant to submit, or the granting body to consider, an application prior to doping control.

• Confidentiality of information: The applicant shall provide written consent for the transmission of all information pertaining to the application to members of the FIFA granting body and, as required, other relevant anti-doping organisations under the provisions of the FIFA Doping Control Regulations.

• An application for a TUE will not be considered for retroactive approval except in cases where:
  a. Medical condition was necessary, or
  b. Due to exceptional circumstances, there was insufficient time or opportunity for an applicant to submit, or the granting body to consider, an application prior to doping control.

• Confidentiality of information: The applicant shall provide written consent for the transmission of all information pertaining to the application to members of the FIFA granting body and, as required, other relevant anti-doping organisations under the provisions of the FIFA Doping Control Regulations.

WADA has established two different TUE forms to be selected and used according to the treatment which has to be administrated to the player (Table 2).

Table 1: Therapeutic Use Exemption procedure

<table>
<thead>
<tr>
<th>For</th>
<th>TUE application to be addressed to</th>
<th>Request made by</th>
</tr>
</thead>
<tbody>
<tr>
<td>National players participating in domestic competitions only. (This includes friendly matches abroad)</td>
<td>FIFA member association, national anti-doping organisation (NADO), or competent public authority association</td>
<td>Player and club doctor</td>
</tr>
<tr>
<td>International players called up to participate in international teams competitions and international friendly matches</td>
<td>FIFA/confederations</td>
<td>Player and national team doctor</td>
</tr>
<tr>
<td>International players participating in club competitions</td>
<td>FIFA/confederations</td>
<td>Player and club doctor</td>
</tr>
<tr>
<td>International players called up by member association in FIFA competitions (i.e. 2006 World Cup qualifiers)</td>
<td>FIFA</td>
<td>Player and national team doctor</td>
</tr>
</tbody>
</table>

Table 2: Requirements for abbreviated and standard TUE

<table>
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<tr>
<th>Abbreviated TUE</th>
<th>Standard TUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>For any treatment involving a substance or method on the prohibited list that is not admissible for an abbreviated TUE.</td>
<td>For any treatment involving a substance or method on the prohibited list that is not admissible for a TUE.</td>
</tr>
<tr>
<td>Use the abbreviated TUE form.</td>
<td>Use the standard TUE form.</td>
</tr>
<tr>
<td>Granted automatically upon receipt of the completed application by the relevant organisation.</td>
<td>Will be examined by the TUEC.</td>
</tr>
<tr>
<td>(Check by the TUEC may be carried out at any time during the duration of the TUE).</td>
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</tbody>
</table>

In order to avoid misunderstandings, players and team doctors were told that a TUE request may be submitted to only one body at a time. The same TUE request may NOT be submitted to several bodies.

To deal with these TUE requests, FIFA and the confederations have created, according to the WADA International Standard, their own panel of independent doctors called the Therapeutic Use Exemption Committee (TUEC). This committee reviews each request and analyses the medical evidence before granting a TUE.
Abbreviated TUE

Abbreviated TUE requests are valid as soon as FIFA, the confederations’ or the member associations’ TUE Committee has received a request and therefore the treatment may start immediately after this is received. However, the TUE Committee has the right to ask for additional information should the indication for application of glucocorticosteroids or beta-2 agonists appear doubtful. FIFA has also decided that for a TUE for beta-2 agonists following the clinical diagnosis of exercise-induced or allergic asthma, functional lung-test results must also be supplied to substantiate the clinical diagnosis. With this request, the FIFA Sports Medical Committee has clearly stressed the importance of sound clinical diagnosis following state-of-the-art assessment to avoid abuse of beta-2 agonists without a clear clinical diagnosis. In this respect, FIFA endorses the statement made by the IOC medical committee workshop on asthma and beta-2 agonists in May 2001.

Standard TUE

In cases of standard TUE where specialised expertise is required, the TUE Committee appoints external independent experts to seek a second opinion to justify the decision.

Standard TUE requests are valid as soon as FIFA or a confederation has sent the player a certificate of approval (except in rare cases of an acute life-threatening condition, for which retrospective approval may be considered).

Results of Current Procedure

The process of Therapeutical Use Exemption has been systematically introduced in the FIFA member associations and the confederations since 2003 after the presentation of the World Anti-Doping Code. FIFA receives applications for TUEs from players participating in international competitions such as qualifying matches for the World Cup (male and female) and various age-category competitions, as well as for the final competition of the World Cups. UEFA, on the other hand, receives requests for confederation competitions such as EURO 2004 and international club competitions such as the Champions League. The total amount of abbreviated and standard TUEs approved by FIFA and UEFA is summarised in Table 3.

The application process has been introduced in such a way so that there is a mutual recognition of the approvals by member association, confederation and FIFA. However, FIFA, if informed, checks the application and decision of member associations and has the right of appeal. Once TUE-approved, the confidential medical information is filed at FIFA and a copy of the approval is supplied to WADA according to the World Anti-Doping Code’s international standard for therapeutic use exemption.

Table 3: Documentation of approved TUEs in FIFA and UEFA

<table>
<thead>
<tr>
<th>Year</th>
<th>Abbreviated TUEs</th>
<th>Standard TUEs</th>
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<tr>
<td>FIFA</td>
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<td>2005</td>
<td>299</td>
<td>101</td>
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http://www.fifa.com/

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Beta-2 Agonists and Asthma
Beta-2 Agonists and Asthma

Asthma is one of the most frequent chronic diseases. Hippocrates already described it in classical antiquity. An inflammation and hyper-responsiveness of the airways to different stimuli occurs. This results in a variable and reversible bronchoconstriction. Although the adult population frequency amounts to approx. 5%, a frequency of 10-15% is assumed in athletes. Pollutants such as nitrogen oxides, ozone, and dust in the air are the main causes of the worldwide increase in observed asthma. There is a genetic predisposition. Asthma is frequently hereditary with typical cases of onset during infancy. However, non-allergic asthma usually arises during adulthood. The factors inducing an asthma attack are numerous: pollen, dust, contact with animals or chemicals at the workplace, medicines (e.g. acetylsalicylic acid, non-steroidal anti-inflammatory drugs), viral infections, cold air, psychological and physical strains.

Exercise-induced asthma is the term given to asthma which only occurs during physical strain. The inhalation of large volumes of cold dry air with the subsequent development of a bronchial mucous membrane edema seems to play a substantial role. The symptoms are normally pronounced towards the end of strenuous physical loads, so that complaints during games of sport usually arise during the intervals. Breathlessness, rhonchus and coughing are typical symptoms. Athletes participating in winter sports are more frequently affected than those in summer sports. Endurance athletes also suffer more frequently from asthmatic complaints than other sportsmen. Despite favourable humid conditions apparent in swimming, the frequency of exercise-induced asthma is particularly large. Competitive swimmers who train several hours a day inhale substantial quantities of chlorine gas, which can cause asthma attacks.

Asthma Therapy

For the treatment of asthma, including exercise-induced asthma, stage patterns exist. For the athletes, the goal of therapy consists of being symptom-free and being able to exhibit normal lung function during all sports activities. When asthma only occurs rarely or intermittently, asthma therapy consists of being symptom-free and being able to perform as well as muscle strength on highly trained athletes.

Asthma Diagnosis

Respiratory symptoms may have many causes. A physiologically occurring shortness of breath (e.g. wheezing) is often associated with high-intensity exercise in poorly conditioned individuals, thus leading to a misdiagnosis of asthma. For a reliable diagnosis, lung function tests are necessary. In pronounced cases, a simple spirometry test with measurement of forced expiratory volume for one second (FEV1) is sufficient. This can otherwise be termed as the air volume that can be exhaled after maximum inhalation within the first second (Figure 1). If the FEV1 is reduced and rises after inhalation of a beta-2 agonist by at least 12%, asthma can be assumed. In most cases, particularly with exercise-induced asthma or a hyperregulable bronchial system, provocation tests are necessary. These can be accomplished using exercise tests in laboratory conditions on an ergometer or under sport-specific conditions with field tests, measuring lung function before and after the test. The effort is considered positive if the FEV1 drops by more than 10% after exercise. Another lung function test involves the inhalation of test substances such as methacholine, which induces a bronchoconstriction. When allergy-induced asthma is suspected, allergy diagnostic tests are necessary.

Beta-2 Agonists and Doping

Of the drugs relevant for the treatment of asthma, beta-2 agonists and glucocorticosteroids appear on the list of prohibited substances for sport. For the prophylactic treatment of asthma and exercise-induced asthma, inhalational application is permitted. A Therapeutic Use Exemption (TUE) – in this case an abbreviated TUE – is required by athletes to use these treatments for exercise-induced asthma. Copies of lung function and/or provocation tests (see asthma diagnostics) are required to be enclosed with the application for TUE.

In contrast to glucocorticosteroids, (see the respective article) inhaled beta-2 agonists, or asthma sprays, are not only banned for competition but also for training. Abbreviated TUEs are only possible for the beta-2 agonists formoterol, salbutamol, salmeterol and terbutaline. A salbutamol concentration in the urine of >1000 ng/ml is usually not reached by inhalational application and is therefore considered a positive doping test. Athletes seeking a competitive advantage, even after allowing for commonly existing medical conditions, frequently abuse inhaled beta-2 agonists. But do asthma sprays actually affect performance? Since 1983, numerous placebo-controlled studies have been published, which have looked at the effect of inhaled beta-2 agonists (including the four mentioned above) on the aerobic and anaerobic performance as well as muscle strength on highly trained athletes. Most studies did not show any increase in performance. In contrast to inhaled beta-2-agonists, oral administration of salbutamol and clenbuterol can induce ergogenic effects, most of the relevant findings, however, originate from animal experiments, with only a few test results coming from those on humans. Overdoses may cause side-effects such as heart palpitations, tachycardia, tremor or rhythm disturbances. Altogether, on the basis of scientific evidence, inhaled beta-2 agonists do not have a performance-enhancing effect in non-asthmatic competitive athletes. one does not have to be asthmatic in order to succeed.

The administrative expenditure for acquiring special permission is substantial. The proof of an asthma illness in need of treatment by means of lung function and provocation tests requires a specialised medical investigation in several athletes. This can cause considerable costs. Therefore, campaigns to clear up the sense and nonsense of asthma sprays would seem highly desirable.

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Figure 1:
- Forced inspiratory volume in 1 sec (FEV1): Normally, after maximal inspiration, at least 80% of the volume is expired again within 1 sec (black curve). With asthma and exercise-induced asthma the volume expired out in 1 sec is decreased (red curve).
- Forced expiratory volume in 1 sec (FEV1): Normally, after maximal inspiration, at least 80% of the volume is expired again within 1 sec (black curve). With asthma and exercise-induced asthma the volume expired out in 1 sec is decreased (red curve).
- FEV1(Asthma)
- FEV1(normal)
Glucocorticosteroids
Hormones are produced in the adrenal cortex, which are described as corticosteroids. Glucocorticosteroids represent a sub-group whose name indicates their main effect: carbohydrate metabolism. This leads to sugar or glucose formation, i.e. from protein and their amino acid constituents. This procedure is called gluconeogenesis. The most physiologically significant glucocorticosteroid is cortisol. Synthetic glucocorticosteroids are often called cortisones.

**Effects**

Cortisone affects metabolism and glucose is formed from proteins. Due to their proteolytic effect, glucocorticosteroids belong to the catabolic hormones. In addition, fat metabolism is affected, which leads to an increased formation of free fatty acids. The most important effects on the electrolyte balance consist of the fact that sodium together with water in the body is held back and potassium is increasingly eliminated. After all, the glucocorticosteroids are of crucial importance for the life-saving stress reaction of the organism.

The broad therapeutic use of cortisone (Table 1) results from the anti-inflammatory characteristics on cells and tissues. Early (edema) and late (e.g. growth of connective tissue cells) inflammatory reactions are inhibited. During sport injuries and symptoms of overuse, inflammatory reactions arise causing pain. Local cortisone injections inhibit inflammation resulting in pain-relieving effect. For some internal and general medical illnesses, cortisone belongs to the necessary drug therapy. With competitive and top-class athletes, a cortisone treatment can, for example, be indicated with allergies, asthma, intestinal diseases or diseases of the skin and eyes (Table 1). With asthmatic diseases, inhalational cortisone treatment belongs to basic therapy.

**Side-Effects**

The frequency of unwanted effects correlates with the duration and dose of the treatment. Table 2 lists important side-effects, particularly in view of sport. It is, however, a selection and is therefore not complete.

The production and release of glucocorticosteroids is controlled by the brain (hypothalamic-pituitary axis). After cortisone treatment, endogenic production is decreased due to the inhibition of this automatic control loop system. This leads to temporary adrenocortical insufficiency. Conditions of exhaustion to the point of collapse in stressful situations can occur after sudden cessation of the cortisone treatment. Furthermore, withdrawal symptoms can develop, accompanied by fever, joint and muscular pains and a general feeling of sickness. Cushing’s Syndrome is assumed if the cortisone therapy leads to symptoms of acne, weight gain, water storage and high blood pressure.

The influence of cortisone on metabolism can also lead to practically relevant side-effects. Due to the new formation of glucose, diabetes mellitus can develop or an existing diabetes can get worse. The protein balance is also adversely affected. The presence of protein is reduced, particularly in the musculature, bone and skin. The myopathy occurring in some cases can be the cause...
of muscle weakness, in particular of the upper arms and thighs as well as the shoulder girdle and pelvic area. In addition, osteoporotic changes of the bone, i.e. a reduction of the bone mass which can lead, for example, to compression fractures of the vertebral bodies, are caused by proteolytic metabolism. Furthermore, the increased calcification induced by cortisol seems to play a part in the osteoporosis. Back pains, for example, can be a consequence of cortisone therapy. Disturbances of wound healing as well as an atrophy of the skin are primarily the result of an inhibition of the connective tissue fibroblasts. A possible resulting loss of potassium would primarily affect the intracellular potassium content and is not always identifiable in measured potassium values in the blood. The anti-inflammatory effect and the weakening of the immune system cause an increase in risk of infection due to cortisone treatment. Inflammatory reactions need to belong to a functional immune system. Cortisone also inhibits parts of cellular immunity. The lymphocytes, including their subpopulations in particular, are attenuated.

Gastric and duodenal ulcers are primary side-effects in the digestive tract. Bleedings and perforations are particularly feared, these complications commonly develop insidiously. A decreased protection of the mucosa is usually considered as the main cause. Ulcers occurring during cortisone treatment should be taken seriously. After all, cortisone can also lead to different psychological disturbances: nervousness, sleep disturbances, listlessness, euphoria and psychoses. The same unwanted effects as with a systemic treatment can in principle occur with a local cortisone therapy. The risk of infections always exists with intra-articular application (injection into the joints), in particular when taking immune system impairment through cortisone into account. Complications such as tendon ruptures can occur when repetitive, local pain injections are administered after sports injuries and repetitive stress reactions. The local administration e.g. of ointment or cream can also cause damage to the eyes and skin. Along with the above-mentioned skin atrophy, the occurrence of acne is also common.

Treatment with Cortisone Preparations

Many cortisone preparations are available. They can be applied in different ways: as injections, tablets, drops, solutions, suppositories, sprays, ointments and/or creams. In principle, even with local use, an absorption into the circulation and therefore into the blood must be taken into account. This leads to systemic reactions as well as the occurrence of the whole spectrum of side-effects. Inhalation treatment, such as that for asthma, seems to produce few systemic effects. Substantial qualitative differences in effect do not exist between the individual preparations. There are, however, quantitative differences, i.e. different efficacies. The biological half-life, or how fast the active substance is broken down or excreted from the body, is of considerable importance. There are substantial differences, particularly in the necessary treatment of athletes subject to doping controls, where this is significant. Between short and long-acting medication, all gradations exist, whereby the latter can still be traced several weeks after the last application. Precise data are not always possible. In German high-performance sport, the active substances Triamcinolone and Dexamethasone are frequently used with orthopaedic indications.

Cortisone and Doping

All glucocorticosteroids are prohibited in competition when administered orally, rectally, intravenously or intramuscularly. Their use requires a Therapeutic Use Exemption (TUE) approval. There exists, however, a frequent, particularly orthopedic, indication for their use. For non-systemic application (e.g. injections into the joints or at tendinous insertions) a simplified procedure corresponding to a de facto message (notification) at the time of application exists, but in each case before competition. This notification requires an abbreviated Therapeutic Use Exemption. Non-systemic applications (topical preparations) when used for dermatological (e.g. ointments and creams), aural/otic, nasal, buccal cavity and ophthalmologic disorders are not prohibited and do not require any form of Therapeutic Use Exemption. The way in which the active substance was administered cannot be differentiated by urine analysis. Therefore, it cannot be distinguished between systemic and non-systemic application.

The different detection times of different preparations are problematic. In order to protect the athletes, it would therefore be necessary to start the application procedure if the local injection of glucocorticosteroids already took place weeks before the next match although usage is not prohibited out of competition. This formal procedure would only be redundant if one is sure that the administered cortisone was no longer traceable after a few days and cannot be detected in the urine at the day of the match.

Performance-enhancing effects of glucocorticosteroids are disputed and have not been proven by scientific data as yet. The euphoric effect is being discussed as a possible mechanism for influencing achievement, but the catabolic effects of long-term use can be unfavourable to performance.
Medical Legal Aspects
Medical Legal Aspects of Doping in Football

Historical Background

Ancient Greek athletes are known to have used special diets and stimulating potions to fortify themselves. Stramonium, caffeine, cocaine, and alcohol were often used by cyclists and other endurance athletes in the 19th century. Thomas Hicks ran to victory in the Olympic marathon of 1904 in Saint Louis with the help of raw egg, injections of stramonium, and doses of brandy administered to him during the race. By the 1920s it had become evident that restrictions regarding drug use in sports were necessary.

In 1928 the International Amateur Athletic Federation (IAAF) became the first international sport federation to ban the use of doping (use of stimulating substances). Many other international federations followed suit, but restrictions remained ineffective as no tests were performed. The death of Danish cyclist Knud Enemark Jensen during competition at the Olympic Games in Rome 1960 – the autopsy revealed traces of amphetamine – increased the pressure for sports authorities to introduce drug tests.

In 1966 the International Cycling Union (UCI) and in 1970 the Fédération Internationale de Football Association (FIFA) were among the first international sports federations to introduce doping tests in their respective World Championships. In the following year the International Olympic Committee (IOC) instituted its Medical Commission and set up its first list of prohibited substances. Drug tests were first introduced at the Olympic Winter Games in Grenoble and at the Olympic Summer Games in Mexico in 1968 after the urgency of anti-doping work had been highlighted by another tragic death, that of cyclist Tom Simpson during the Tour de France 1967.

A reliable test method to detect anabolic steroids was finally introduced in 1974 and the IOC added anabolic steroids to its list of prohibited substances in 1976. This resulted in a marked increase in the number of drug disqualifications in the late 1970s, notably in strength-related sports such as throwing events and weightlifting. Blood boosting or blood doping which involves removal and subsequent re-infusion of the athlete’s blood in order to increase the level of oxygen-carrying haemoglobin, has been practiced since the 1970s. The IOC banned blood doping as a method in 1986.

Anti-doping work was complicated in the 1970s and 1980s by suspicions of state-sponsored doping practiced in some countries. The most famous doping case of the 1980s concerned Ben Johnson, the 100-metre runner who tested positive for stanozolol (anabolic steroid) at the Olympic Games in Seoul, 1988. Johnson’s case focused the world’s attention to the doping problem to an unprecedented degree.

In 1998 a large number of prohibited medical substances were found by the police in a raid during the Tour de France. The scandal led to a major reappraisal of the role of public authorities in anti-doping affairs. As early as 1963, France had been the first country to enact anti-doping legislation. Other countries followed suit, but international cooperation in anti-doping affairs was long restricted to the Council of Europe. In the 1980s there was a marked increase in cooperation between international sports authorities and various governmental agencies. Before 1998 debate was still taking place in several discrete forums (IOC, Sports Federations, individual governments), resulting in differing definitions, policies, and sanctions. One result of this confusion was that doping sanctions were often disputed and sometimes overruled in civil courts.

The Tour de France scandal highlighted the need for an independent international agency, which would set unified standards for anti-doping work and coordinate the efforts of sports organizations and public authorities. The IOC took the initiative and convened the World Conference on Doping in Sport in Lausanne in February 1999. Following the proposal of the Conference, the World Anti-Doping Agency (WADA) was established on 10 November 1999.

On March 5, 2003, at the second World Conference on Doping in Sport, some 1200 delegates representing 80 governments, the IOC, the International Paralympic Committee (IPC), all Olympic sports, national Olympic and Paralympic committees, athletes, national anti-doping organizations, and international agencies supported the World Anti-Doping Code as the basis for the fight against doping in sport. The Code entered into force on January 1st, 2004.

On October 19, 2005, the World Anti-Doping Code was adopted as the 1st International Convention against Doping in Sport by the General Conference of UNESCO at its plenary session. Some 184 countries have signed the Copenhagen Declaration on Anti-Doping in Sport, the political document through which governments show their intention to implement the World Anti-Doping Code by the ratification of the UNESCO Convention.

Doping Control in Football

FIFA introduced an anti-doping program in 1970 at the World Championships, being one of the first international sports federations to do so. The fundamental aims as stipulated in the FIFA Doping Control Regulations (2006) are quite similar to the purpose of the World Anti-Doping Code Program set out below.

Definitions

The word doping is probably derived from the old Dutch word ‘dop’, which was the name of an alcoholic beverage made of grape skins used by Zulu warriors in order to enhance their prowess in battle. The term progressed into mainstream use in the early 20th century, originally referring to drugging of racehorses. The practice of enhancing performance through foreign substances or other artificial means, however, is as old as competitive sport itself.

According to the definition of doping in the World Anti-Doping Code, doping is defined as the occurrence of one or more of the following violations:

- The presence of a prohibited substance or its metabolites or markers in an athlete’s bodily specimen (strict liability rule)
- Possession by an athlete at any time or place of a substance that is prohibited in out-of-competition testing or a prohibited method, unless the athlete establishes that possession is pursuant to a therapeutic use exemption granted in accordance with the FIFA Doping Control Regulations regarding the therapeutic use of forbidden substances or other acceptable justifications
- Possession of a substance that is prohibited in out-of-competition testing or a prohibited method by athlete support personnel in connection with an athlete, competition or training, unless the athlete support personnel establishes that the possession is pursuant to a Therapeutic Use Exemption as described previously.
- Trafficking in any prohibited substance or prohibited method is still a violation of the anti-doping regulations and in most legal systems an illegal act against the medical preparations law.
- Administration or the attempted administration of a prohibited method to any athlete, or assisting, encouraging, aiding, abetting or covering up as well as any other type of complicity involving an anti-doping rule violation or any attempted violation.

As set forth in the preamble of the World Anti-Doping Code, the purposes of the World Anti-Doping Program are:

- To protect the athletes’ fundamental right to participate in doping-free sport and thus promote health, fairness, and equality for Athletes worldwide; and
- To ensure harmonized, coordinated, and effective anti-doping programs at the international and national level with regard to detection, deterrence, and prevention of doping.

Prohibited substances in the context of these regulations are regularly published in the:
- WADA (World Anti Doping Agency) list of prohibited substances (http://www.wada-ama.org) and
- are included as Appendix A of the FIFA Doping Control Regulations (www.FIFA.com)
Medical Legal Implications

Strict Liability Rule
The reason for the strict liability rule has been comprehensively stated by the Court of Arbitration for Sport (CAS), Lausanne in certain cases e.g. the case of Quigley v. International Shooting Union (UIT) in 1995:

“It is true that a strict liability test is likely in some sense to be unfair in an individual case, such as that of Quigley, where the athlete may have taken medication as the result of mislabelling or faulty advice for which he or she is not responsible – particularly in the circumstances of sudden illness in a foreign country. But it is also in some sense unfair for an athlete to get food poisoning on the eve of an important competition be altered to undo unfairness. Just as the competition will not be postponed to await the athlete’s recovery, so the prohibition of banned substances will not be lifted in recognition of its accidental absorption. The vicissitudes of competition, like those of life generally, may create many types of unfairness, whether by accident or the negligence of unaccountable persons, which the law cannot repair.

Furthermore, it appears to be a laudable policy objective not to repair an accidental unfairness to an individual by creating an intentional unfairness to the whole body of other competitors. This is what would happen if banned performance-enhancing substances were tolerated when absorbed inadvertently. Moreover, it is likely that even intentional abuse would in many cases escape sanction for lack of proof of guilty intent. And it is certain that a requirement if intent would invite costly litigation that may well cripple federations – particularly those run on modest budgets – in their fight against doping.”

The Whereabouts Rule
Apart from such special cases, effective doping controls are bonded to out-of-competition tests. Without accurate athlete location information such controls may be inefficient and sometimes impossible. This so called “whereabouts rule” requires athletes and/or teams that have been identified for out-of-competition control to be responsible for providing and updating information on their whereabouts so that they can be located for No Advance Notice out-of-competition control. The applicable requirements are set by the responsible sport federation or National Anti-Doping Organisation (NADO) in order to allow flexibility based upon varying circumstances encountered in different sports and countries. A violation of this rule may be based on either intentional or negligent conduct by the athlete, but it is known that the whereabouts rule may not be realistic in international team sports, if players are normally playing for a club far from their home nation.

Separation of Power
An important legal principle is the separation of power between the anti-doping executive authorities and the disciplinary committee responsible for the administration of anti-doping sanctions. This is to minimise any accusations of bias or conflict of interest in the application of the Code.

Under FIFA regulations, this principle is applied in a practical sense by having the Doping Control Sub-Committee (representing medical, pharmacological and medical legal expertise) dealing with the medical and biochemical aspects of the alleged doping event and, once this issue has been determined, a separate Disciplinary Committee which awards the appropriate sanction in view of the individual circumstances of the athlete concerned. The exact procedure is described below.

Medical Legal Aspects of Doping Control Procedures
The full details of the FIFA doping control procedure are set out in the annually updated FIFA Doping Control Regulations (http://www.fifa.com/en/regulations/regulation/0,1584,9,00.html)

Regarding the medical legal aspects of doping control procedures, the process is as follows:

• Once an A sample has tested positive, then the FIFA Doping Control Sub-Committee investigates the documentation of the case and prepares a report for the FIFA Chief Doping Control Officer. The FIFA Chief Doping Control Officer has to verify that the correct doping control procedures have been completed according to the doping control regulations. This process usually involves contacting the testing laboratory as well as the original doping control co-ordinator where the athlete was tested.

• If the analysis of specimen A is confirmed as positive by the FIFA Doping Control Sub-Committee’s report, the FIFA General Secretary shall at once confidentially notify the chairman of the Disciplinary Committee, the Sports Medical Committee and the national association of the player concerned, which shall have the right to request a second analysis using specimen B within 24 hours of being notified.
• If a second analysis is requested, FIFA shall communicate this request immediately to the head of the laboratory where the specimen B is being kept. An analysis of specimen B shall be carried out as soon as possible, by personnel who were not directly involved with the analysis of specimen A. The association concerned shall have the right to have a representative present, in addition to the player concerned. The results of the analysis of specimen B shall be sent immediately to the FIFA Chief Doping Control Officer responsible, by fax or e-mail. If no request for a second test is made, the laboratory shall dispose of specimen B after 30 days have elapsed.

In addition to the procedural roles above, the FIFA Chief Medical Officer and the Doping Control Sub-Committee also have to estimate the seriousness of the individual case from a medical point of view as to whether the violation was intentional (partially autonomous but not fully self responsible), deliberate or negligent and examine whether the player is personally guilty of the offence being sanctioned and the unjustness of his behaviour has to be obvious to him. Thus, every sanction inevitably contains a distinctive individual component.

Problems that Remain to Be Solved

With regard to the ongoing development of new substances and laboratory methods, regular review of standards and regulations is necessary for appropriate anti-doping action in accordance with the scientific evidence and sport ethics.

T/E ratio

The lowering of the threshold for the ratio of testosterone (T) to epitestosterone (E) from 6 to 4 has led to intense discussion with the accredited laboratories and raised concerns on behalf of FIFA. According to the FIFA database 2005, none of the samples with elevated ratios between 4 and 6 showed evidence of exogenous intake in the GC-Isotope Ratio Mass Spectrometry (GC-IRMS). In face of the logistic impact and additional costs, FIFA should strongly advocate detailed statistical analysis of the WADA data, examining the incidence of exogenous intake of testosterone in samples with T/E ratios between 4 and 6. Furthermore, legal difficulties arise in cases where the T/E ratio is between 4 and 6 but GC-IRMS does not verify exogenous intake.

Alpha-Reductase Inhibitors

The increasing use of alpha-reductase inhibitors for treatment of male pattern baldness has led to positive urine samples of athletes for finasteride, the main metabolite. Finasteride is a banned substance listed under 55. Diuretics and masking agents in the doping control regulations. Only recently, a German football player has been suspended by the supreme court of the German Soccer Federation for six months with additional fine after a positive result for finasteride. In this case, the laboratory explicitly used more sensitive analytical methods which could not identify any traces of anabolic steroids in the sample – a finding that is not covered by the World Anti-Doping Code. This case illustrates several critical medical legal aspects which have to be addressed, including the question if male pattern baldness represents a psychological disease and the eligibility for a Therapeutic Use Exemption.

Recreational Drugs

Recent years have shown a constant increase of positive testing for recreational drugs. While this finding reveals rather a social than a doping problem, an important legal aspect has to be considered, too: The consumption of marihuana presents a severe offence against the law in some countries, especially in Africa and Asia, even if consumed abroad. Here, the publication of a positive result may lead to serious consequences for the respective player including a prison sentence. Anti-doping bodies should therefore carefully reconsider the unconditioned ban of recreational drugs, preferably based on a juridical expert’s opinion.

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Bundesgericht des Deutschen Fußballbundes DFB

Decision Nr. 3/2005/2006

Conclusion

While the World Anti-Doping Code and the Doping Control Regulations of FIFA offer a comprehensive basis for the fight against doping, the permanent progress in the development of new substances and laboratory methods calls for regular review and update of the adopted policies. Whereas harmonization of the strategies of national and international anti-doping agencies is reinforced, the legislation and politics of different countries constitute a permanent obstacle. Any regulation concerning medical legal aspects should therefore be based on scientific evidence and juridical expertise and has to be supported by close collaboration of national and international bodies.
FIFA's Future Activities in the Fight against Doping
FIFA’s Future Activities in the Fight Against Doping

The fight against doping in sport receives considerable media interest and results in much speculation regarding the ability of athletes to compete on a level playing field. Football was one of the sports that took early leadership in this fight when FIFA introduced doping control in football in 1970 as part of a wider strategy to ensure that the results of representative matches were a fair reflection of the ability of those taking part.

As a result of the collaborative effort between FIFA, the confederations and their member associations and in conjunction with national anti-doping organisations, more than 20,000 doping controls are performed annually on football players. The overall incidence of positive doping samples for prohibited substances accounts for 0.4% of all tests.

The majority of positive drug tests are due to cannabis and cocaine, so-called social drugs. Only a few individual cases (0.07% of positive tests in 2004) were positive for anabolic steroids, such as nandrolone and testosterone.

The majority of doping control tests have been carried out in competition. FIFA, UEFA and some of the national anti-doping organisations also perform unannounced, out-of-competition controls at training venues during the football season. Prior to the 2006 FIFA World Cup™ in Germany, unannounced doping controls were performed in friendly matches between nations as well as during the training camps prior to the opening match on 9 June 2006. All tests to date have proved negative. UEFA, the European football confederation, also performed unannounced testing in the 2005-2006 football season on all of the teams participating in the UEFA Champions league and UEFA Cup. Ten players were randomly selected from each of the 38 top European professional teams and subjected to testing. No prohibited substances were found in any of the 380 samples tested.

Since 1994, FIFA has followed a similar strategy in international competitions for both men and women. In these tests, two randomly selected players per team are tested after each finals match and a total of 3,327 tests have been performed in 32 tournaments to date. Only three samples have tested positive since testing commenced: one for ephedrine, one for cannabis and one for nandrolone. One sample tested positive for ephedrine during the qualifying matches for the 2006 FIFA World Cup Germany™. The incidence of positive tests in FIFA competitions over the past 12 years is 0.1%.

During the Olympic Games in Sydney 2000 and in Athens 2004, none of the football players tested positive for any prohibited substances. An internal survey among all Olympic team sports federations revealed that none of the team sports athletes tested positive for prohibited substances.

It is currently not possible to compare positive drug tests among the different sports as the World Anti-Doping Agency (WADA) only presents adverse analytical findings in their published statistics rather than true positive results. The statistics include ‘therapeutic use exemptions’ as well as elevated (>4) T/E ratios that may be seen in normal athletes. Football accounts for the majority of doping controls performed worldwide.

The current doping statistics demonstrate a very low incidence of positive tests and justifies the assumption that there is no evidence for systematic doping in football and most probably in any of the other Olympic team sports.

Although no clear data exists from WADA about the distribution of in- and out-of-competition drug testing, it can be assumed that the majority are in-competition. Football players worldwide understand that prohibited substances in sport will neither improve their physical performance nor their football skills and hence they are reluctant to use agents that are not effective and subject to possible sanctions.

There are several possible explanations for the low incidence of positive findings of prohibited substances among football players.

• The stringent drug-testing programme occurs during the entire football season in most countries.
• Football players worldwide understand that prohibited substances in sport will neither improve their physical performance nor their football skills and hence they are reluctant to use agents that are not effective and subject to possible sanctions.
• As a result of ongoing education campaigns by FIFA to doctors, administrators, officials and players, a drug-free culture is encouraged in football.

It is also possible that both in- and out-of-competition testing is insufficient to detect drug use. However, this is unlikely given the large number of in- and out-of-competition drug tests occurring at all levels of professional sport over many years with relatively few positive results.

FIFA has also developed close collaboration with the medical representatives of other Olympic team sports federations, as well as with the International Rugby Board, over the past six years, realising that the dimension of abuse of prohibited substances is different in comparison to individual Olympic sports. The medical representatives of these bodies expressed their collective opinion during a WADA meeting in Copenhagen in...
March 2003, suggesting a possible revision of the World Anti-Doping Code given the different needs of international team sports federations and the lack of evidence of systematic doping in those sports.

Furthermore, given that 20,000 doping controls are conducted on football players annually worldwide, it became obvious that a close collaboration had to be developed with the accredited testing laboratories in order to understand the different examination methods and to keep abreast of new scientific developments. The close collaboration with the laboratories has resulted in these laboratories being considered equal partners in the global strategy against doping. It has also resulted in a number of research studies being performed on controversial issues such as nandrolone metabolism, analysis of testosterone/epitestosterone ratio and the influence of age and ethnic differences on testosterone metabolism.

It seems likely that constantly increasing the number of drug tests would not alter the incidence of positive findings. Unannounced testing at training grounds following the impressive example of UEFA with Champions League teams could be introduced in all confederations to provide more information from possible abuse of prohibited substances between official matches. The absence of any positive tests in the UEFA testing to date makes it unlikely that this strategy would identify a significant number of drug cheats who are currently not being detected.

Given these findings, the question is raised as to whether there is a need for fundamental change in the strategy to fight doping in football?

The FIFA Sports Medical Committee is of the opinion that the educational process has to be intensified with the help of national associations and in particular, through team physicians. The team physicians play a central role in the educational programme as they have direct influence over player behaviour and have the knowledge to advise players, not only on the potential risks to health, but also the effect that sanctions may have on a player’s career if caught. The 32 team physicians of the 32 teams of the 2006 FIFA World Cup that were conducted on football players worldwide, it became obvious that a close collaboration had to be developed with the accredited testing laboratories in order to understand the different examination methods and to keep abreast of new scientific developments. The close collaboration with the laboratories has resulted in these laboratories being considered equal partners in the global strategy against doping. It has also resulted in a number of research studies being performed on controversial issues such as nandrolone metabolism, analysis of testosterone/epitestosterone ratio and the influence of age and ethnic differences on testosterone metabolism.

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Given these findings, the question is raised as to whether there is a need for fundamental change in the strategy to fight doping in football?

The FIFA Sports Medical Committee is of the opinion that the educational process has to be intensified with the help of national associations and in particular, through team physicians. The team physicians play a central role in the educational programme as they have direct influence over player behaviour and have the knowledge to advise players, not only on the potential risks to health, but also the effect that sanctions may have on a player’s career if caught. The 32 team physicians of the 32 teams of the 2006 FIFA World Cup that were carried out by members of the international sports federations and obligatory by physicians. There is no need to delegate this important work to commercial companies. The experience of FIFA clearly indicates that employing physicians to perform doping controls is not only effective but can be done at low cost, and most probably, it would reduce the risk of potential corruption as the physicians have to follow their professional ethical and medical legal constraints.

Another challenge is the continuous search to identify new performance-enhancing drugs being distributed on the market via the internet and in this respect, medical science, in close collaboration with laboratory experts and the Scientific Committee of the World Anti-Doping Agency, might help to identify possible new drugs and sanction their abuse accordingly.

Arguably, the major challenge for the future lies in genetic doping and its detection. There is no doubt that we cannot stop the development of medical science as the development of altered genetic information seeks to help many patients suffering from incurable diseases and yet it could be claimed that this scientific advancement might be abused for performance enhancement in sport. In this regard, the education and cooperation of team doctors forms a crucial link in the chain to prevent athletes adopting such strategies.

Future Challenges in the Fight against Doping

In 2006, FIFA launched a new development programme, FUTURO II. The FIFA Sports Medical Committee undertook to implement the mandate of FIFA President Joseph S. Blatter and the FIFA Executive Committee, i.e. to educate more than 3,000 physicians worldwide in football medicine over the next three years. Anti-doping education is an integral part of the instructional courses, which were launched in Oceania in February 2006 followed by CONMEBOL (South America) in April 2006. Active participation within the instructional courses will entitle the physicians to become members of the worldwide network of FIFA medical officers, not only to deal with optimal management and prevention of injuries, but also to act as FIFA doping control officers throughout the 207 member associations of FIFA in collaboration with national anti-doping organisations.

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Conclusion

Following the leadership of FIFA, there is strong evidence that doping controls and sanctions of positive cases will only be sufficient if the problem of doping and recreational drug use is tackled over the long-term in a comprehensive manner. There are strong indicators that the education of athletes, and in particular footballers, using an established medical network might be more effective than punitive sanctions alone. The use of team physicians as a central part of the anti-doping strategy serves not only to create a drug-free sports culture, but through education, it will increasingly improve the overall health management of all athletes.

Furthermore, FIFA encourages other international sport federations and/or national anti-drug organisations to collaborate with the FIFA Sports Medical Committee/ F-MARC and to take advantage of the existing worldwide network of team physicians and doping control officers to institute similar anti-doping processes and strategies in their own sports, and therefore support WADA in its objective – doping-free sport.

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Glossary and Abbreviations
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19-NA 19-Norandrosterone: one of the two major substances remaining after intake and degradation of nandrolone in the body. It can be detected in urine for up to several months with extremely sensitive methods.

19-NE 19-Noretiocholanolone: the second of the two major substances remaining after intake and degradation of nandrolone in the body. It can be detected in urine for up to several months with extremely sensitive methods.

AAS Anabolic-Androgenic Steroids: derivatives of testosterone with performance-enhancing capacity and adverse side-effects (cardiovascular, hepatic, endocrine, reproductive, psychological, tendon injuries) that jeopardise health, forbidden in sports.

ACTH Adrenocorticotropic Hormone or Corticotrophin: this hormone is secreted by the anterior pituitary gland in the brain. Its function is crucial as it stimulates the adrenal cortex to release cortisol, which is a key factor in the body’s metabolism of fats, carbohydrates, sodium, potassium and protein.

Adrenaline The fight-or-flight hormone produced in the adrenal glands. Its effects are rapid heartbeat, increased blood pressure and rapid, shallow breathing as well as releasing glucose into the blood as a readily available source of energy.

Amphetamines Powerful central stimulant, may increase physical energy by stimulating all three energy systems of the body: mental aptitude, excitement and restlessness. Negative effects are anxiety, irresponsible behaviour, irritability, insomnia and depression. Characterised by a fast development of tolerance, inducing dependence with psychosis and aggressiveness. Side-effects include confusion, delirium, hypertension, raising of heart rate and in the long-term, detrimental effects on heart muscle. Has lead to death of athletes due to overheating of the body. Presence of amphetamine in urine is a severe doping offence.

A sample The first of the two urine specimens given by a player to be examined in a laboratory. If it proves positive, the test is performed for a second time before the result is reported to the official authorities.

ATP-CP Adenosine Triphosphate–Phosphate Creatine: this is the very short-term, anaerobic energy system of the body. It effects very powerful muscular contractions sustainable for between 1 and 45 seconds; recovery time for ATP replenishment is usually several minutes.

Beta-2 Agonists Drugs that are also called asthma relievers. They copy some effects of natural hormones like adrenaline, which prepare the body for action. One of these effects is to open up the airways so that more air can reach the lungs. Relievers are used to relieve the symptoms, such as chest tightness, coughing, wheezing and breathlessness.

B sample If the A sample tests positive, a player may request an analysis of his second urine specimen won during the doping control in order to validate the result.

BFU-E Burst-Forming Unit-Erythroid: the first stage of differentiation of progenitor cells committed to become red blood cells.

Caffeine Found in tea, coffee and cola and also an ingredient in common medications, caffeine produces mild stimulation. Since 2004 it is no longer prohibited, but monitored.

Caffeine Chinese hamster ovary tissue is commonly cultured as individual cells in a monolayer and studied worldwide.

Cocaine Most potent natural stimulant obtained from coca species and probably the most addictive agent known. Snorting, smoking and injection of cocaine pose great risks to the user. After an initial rush of well-being, it leaves the user even more depressed than before. No true enhancement of performance, but detrimental effects instead, which lead to control of life by the substance. Highly toxic for the heart with dramatic fatalities reported, even more so if combined with alcohol. Presence of cocaine in urine is a severe doping offence.

CNS Central Nervous System: this term refers to the brain and the spinal cord as opposed to the peripheral nerves.

Crack Cocaine in a processed form used for smoking.

DCO Doping Control Officer: specially trained physicians who conduct doping controls on behalf of FIFA.

DHA Dihydropiandrosterone: endogenous (produced within the human body) steroid, responsible for the development of the external genitals in the male foetus.

DHEA Dehydroepiandrosterone: endogenous (produced within the human body) steroid.

Diuretics Substances that enhance urine excretion

Ephedra alkaloids Naturally occurring stimulants obtained from plants, examples are ephedrine, pseudoephedrine, norpseudoephedrine, methylpseudoephedrine and methylxylpseudoephedrine.

Ephedrine Mixed sympathomimetic agent that leads to increased cardiac output, but also vasocostriction resulting in high blood pressure and heart rate. Isolated use leads to only inconsistent ergogenic benefit for power, endurance and muscle strength. Combination with vitamins, minerals or caffeine in studies results in increased energy, metabolism and fat loss and increased time to exhaustion and improved muscle strength. Potential health risks are considerable, overdose most dangerous because of irregular heart beat, risk of myocardial infarction, seizures and eventually death. Medical use is tolerated, but urine concentration of >10 μg/mL constitutes a positive doping test.

Epinephrine Adrenaline, hormone produced by the adrenal glands, (cf. Adrenaline).

EPO Erythropoietin: hormone that is produced by special cells in the kidney and the liver in response to hypoxia and promotes the development of red blood cells in the bone marrow. Normally, if oxygen delivery increases, this leads to a reduction of EPO, thereby keeping the red blood cell amount in a steady-state. Because of its ergogenic capacity, this hormone is used illicitly in endurance sports: its detection depends on investigation of blood samples.

CAS Court of Arbitration for Sport: the Court of Arbitration for Sport (“CAS”) is an independent institution that was created in 1983 to settle sports-related disputes.

CFU-E Colony-Forming Unit-Erythroid: stage of commitment of progenitor cells following the stage of BFU-E, constituting a major stage in the maturation process of red blood cells.

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GLOSSARY AND ABBREVIATIONS

Erythropoiesis: Process of development of mature red blood cells (erythrocytes).

FDA: Food and Drug Administration: government agency responsible for regulating food, dietary supplements, drugs, medical devices and blood products in the United States.

FDC: FIFA Disciplinary Code

Ferritin: Protein that stores iron in the body. The serum ferritin level, which is the amount of ferritin in the blood, is directly proportional to the amount of iron stored in the body.

FEV1: Forced Expiratory Volume for one second: the volume of air you can breathe out in one second, which is reduced if someone has an obstructive lung disease like asthma.

FIFA: Fédération Internationale de Football Association

F-MARC: FIFA Medical Assessment and Research Centre

GC-MS: Gas Chromatography-Mass Spectrometry: a method that combines the features of gas-liquid chromatography and mass spectrometry to identify different substances within a urine sample. As a specific test, it actually identifies the presence of a particular substance in the sample.

GC/IRMS: Gas Chromatography/Combustion/Isotope-Ratio-Mass-Spectrometry: method to determine the isotopic composition of a specimen by gas chromatography followed by combustion to CO2 and finally mass spectrometric analysis. Atoms of carbon occur in nature with different weights; these are known as isotopes. Their proportion in any substance varies according to its origin. Carbon isotopes found in endogenous and exogenous steroids differ, which therefore allows a direct confirmation of an intake of steroids. This test may be used after inconclusive T/E results (cf. IRMS).

GHB: Gamma-hydroxybutyrate: synthetic drug used as an anaesthetic, but also used by bodybuilders because it is supposed to promote the kind of sleep that is best for protein and therefore muscle build-up.

GHRH: Growth Hormone Releasing Hormone: hormone released by the hypothalamus that stimulates growth hormone secretion.

Glucocorticosteroids: Hormones that are produced in the adrenal cortex and regulate the carbohydrate, fat and protein metabolism. They also affect muscle tone and the microcirculation and inhibit inflammatory, allergic, and immunologic responses. In humans, the most important ones are cortisol, cortisone and corticosterone.

Haematopoiesis: Process of development of mature blood cells. Rare pluripotent stem cells proliferate and differentiate into all cells that can be found in blood and lymphoid organs.

HDL: High Density Lipoprotein: fraction of lipids in the blood that carry cholesterol from the body's tissues to the liver. Because they can remove cholesterol from atheroma, which might obstruct arteries, and transport it back to the liver, they are considered “good” lipoproteins.

HGF: Human Growth Hormone: endogenous hormone produced by the pituitary gland. Some positive effects on muscle mass, but true performance-enhancing effect difficult to evaluate. Long-term adverse effects unknown, acromegaly is feared because of coarsened facial appearance, arthralgias, fluid retention, swelling of hands and feet and an increased risk of diabetes and hypertension, osteoporosis and others. Detection in urine has considerable limitations, therefore methods for the determination of a specific ratio in the blood have gained acceptance. They may differentiate endogenous from injected forms.

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NADO | National anti-doping organisation

Nandrolone | 19-Nortestosterone: one of the most widely used synthetic AAS by athletes, because a small chemical modification makes it more anabolic than androgenic, thereby reducing the main negative side-effects. Nandrolone is dangerous and forbidden in sport. Danger of contamination of supplements, especially creatine products, with nandrolone.

ng | Nanogram: unit used for standardised declaration of the concentration of substances in specimens.

OFF-model | In anti-doping test screening for EPO-abuse, multiple markers in the blood are measured and combined in a special mathematical model, thereby allowing to identify players who have taken rhEPO in recent days.

ON-model | In anti-doping test screening for EPO-abuse, multiple markers in the blood are measured and combined in a special mathematical model, thereby allowing to identify players under rhEPO treatment.

Pituitary gland | Also pituitary appendage, this controls the functions of the other endocrine glands in the body. The pituitary gland is no larger than a pea and is located at the base of the brain. It has three sections: the anterior, the intermediate and the posterior lobe, each of them producing different hormones.

Psychomotor stimulants | Group of drugs, including cocaine, amphetamine, and ephedrine that produce wakefulness and arousal, and stimulate behaviour.

RIA | Radio-Immunoassay: Method to determine the quantity of a substance by use of a specific radioactive antigen


Selegine | Derivative of amphetamine, forbidden in sport.

sTFR | Serum Transferin Receptor: the soluble transferin receptor is a means to differentiate between iron deficiency anaemia and anaemia of chronic disease.

sTFR/Ferritin-ratio | This index was used for detection of EPO doping but has been modified to the sTFR/total protein ratio in order to take into account exercise-induced concentration of the blood.

Stimulants | These substances stimulate the central nervous system and are sometimes referred to as “uppers”. They reverse the effects of fatigue on both mental and physical tasks, increase alertness, competitiveness and aggression. This action calls for relatively high doses, which carry the risk of side-effects. They are differentiated into psychomotor stimulants, sympathomimetics and miscellaneous stimulants.

Sympathomimetics | Class of drugs that mimics effects of a stimulated sympathetic nervous system. As such, they increase cardiac output, dilate bronchioles and usually produce constriction of blood vessels.

Testosterone | Steroid hormone, regulates physiological processes in the male including muscle protein metabolism, sexual and cognitive functions, erythropoiesis, lipids and bone metabolism.

TUE | Therapeutic Use Exemption: in players who suffer from a disease and require medical treatment, drugs containing prohibited substances can be permitted if the player’s health would be impaired if the drug were withheld, performance is not enhanced by its correct use and no permitted alternative drug is available. This exemption has to be requested in advance. An abbreviated TUE will be granted automatically upon receipt, a standard TUE will be examined by the TUEC (see below).

TUEC | Therapeutic Use Exemption Committee: Panel of independent doctors created by FIFA and the confederations. These committees review each respective request for a TUE and analyse the medical evidence before granting it.

UEFA | Union of European Football Associations

VO2 max | Volume of oxygen consumed during intense, whole-body exercise at maximum capacity. This volume is measured as a rate of either litres per minute or ml/litres per kilogram bodyweight per minute. Since the oxygen consumption is directly related to the energy expenditure, the VO2 max gives a good indication of the maximal capacity of a player to exercise aerobically.

WADA | World Anti-Doping Agency