DOPING – SUBSTANCES WITH HORMONAL AND BIOLOGICAL EFFECTS

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Abstract: The paper deals with sports doping as a negative phenomenon in society. Characterization, distribution, and abuse of substances with hormonal and biological action in addition to androgenic anabolic steroids. In the introduction of the article we discuss the history of the concept of doping and its explanation in terms of several perspectives. There is a large number of substances with hormonal effects, so the paper focuses on their distribution and description of their negative properties on the human body in the context of legislation in force in Slovakia and from the point of view of forensic chemistry.

Key words: doping, anti-doping, sport, health, substances, hormonal effect, biological effect.

INTRODUCTION

In the beginning of the 20th and 21st century came the sports, but also in other areas of human activity big increase of demands to the indivbiduals and society. In sport, it is an extreme competition that places high requirements on mental and physical activity and the readiness of athletes in order to achieve the best results, break sports records, beat opponents and win. However, we take this for granted, because sport must have a sense of ethics, fair play, honesty, excellent performance, character, joy, fun, teamwork, dedication, linkage, respect for rules and laws, respect for oneself and other participants, courage, cohesion and solidarity. It is well known that sports competition is a global phenomenon that breaks down borders between countries. At the same time, we must accept the fact that sporting activity is facing new threats and challenges that have emerged in society. These include commercial pressure, abuse of young athletes, doping, racism, violence and money laundering.

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We agree with the opinions of the authors (Rondová & Kasinec, 2015), who note that the professional sport is no longer a context of social prestige, when athletes performed their profession with pride and the price was mainly the feeling of victory, or modest financial evaluation. Modern sport has become an implement for raising large amounts of money, regardless of the tools, methods and damage involved, and that is why we often see various sports scandals, often celebrities, who, under public pressure, admit to using banned doping substances, for example.

The best athletes, coaches, sports managers cannot forget one of the main facts, which results from their social status, that they represent an ideal for young people to achieve sports success, they are strong role models that motivate young people (active as well as passive athletes). Any sport scandal, which is not eligible and is caused by inappropriate observance by a top athlete (e.g. exposed doping) sheds a very negative light on all the attributes of the sport we have known since ancient times.

The result is also a negative situation, where allowed or not allowed resources are also used by recreational sports amateurs in order to shape their body according to their own idealized idea, quickly gain excellent condition, muscle mass and improve overall physical and mental performance. It is striking that this problem affects younger and younger boys and girls (Rondová & Kasinec, 2015: 89). Therefore, in the next part of our paper we will focus on the issue of doping and anabolic androgenic steroids.

DOPING – CHARACTERIZATION

Nowadays we know several theories that try to explain the origin of the term doping. Kuklík and the collective state (2012) in their publications that in the 18th century the South African Kafrov tribe used the word "dop" for an invigorating alcoholic drink that they drank during a religious ceremonial dance. The Zulu tribe prepared a drink from grapes and cola to improve physical performance in battle. Extract from the plant Cola nitida and Cola accuminata was also commonly drunk in West Africa during running or walking competitions. American slang has been enriched by the term "doop" by Dutch colonizers, which means "strong sauce". It was a special mixture of tobacco and Datura stramonium. The plant is toxic with the atropine alkaloid and has a sedative effect, whis is causing hallucinations and confusion. In 1889, the word "dope" was first used to prepare viscous opium for smoking, and in the 1990s it was used for all narcotics. Later, this term was introduced to name not only narcotics, but also many other substances, while in the field of sports, the word took the form of "doping". The word "doping" can also be found in the English dictionary as early as 1889, and its definition expresses a special mixture of opium and narcotics for racehorses.

In the broader knowledge of the literature (Štáblová, Brejcha et al., 2006), we discover cognition about doping in antiquity and the Middle Ages, where, in addition to athletes (Olympians), doping agents were used by dukes and gladiators who drank supportive drinks to stimulate their aggression, overcome fatigue and reduce pain after injury. History indicates that coaches who focused on long-term physical training of athletes had knowledge of the effect of diet on their mental and physical readiness for the Olympics (they ate dried figs and drank herbal concostions to bleed some internal organs). It is also interesting to note that in the 18th century, when the main power of the Church declined, there was a freer scientific and technical development and with it a new era of doping. We can therefore say that since the 18th century there is a period when new synthetic substances used as doping come to the fore, and in the 19th century many chemicals are already known which have found application in this area. We give an example as early as 1886, when a cyclist died at the Paris-Bordeaux race as a

result of doping drug overdose, resp. almost a hundred years later (1967), an English racer Simpson died during an amphetamine overdose during the Tour de France.

It is necessary to emphasize that from the basic interpretation of the concept of doping and the historical analysis of the issues related to it, we can say that doping (the use of specific chemical substances) is about influencing, increasing physical or mental activity of a living organism in order to achieve better physical or mental performance (muscle growth, increasing sports performance, concentration, pain relief, changes in perception of reality, etc.).

The word doping can be found in the literature in several interpretations. Žilinka and Motyčík (2015) define the term as follows: "Doping - the use of prohibited pharmacological substances and methods. A phenomenon that is contrary to the "spirit of sport", i.e. such values as strengthening health, ethics, honesty, respect, fair play, teamwork or solidarity. A phenomenon that attacks the ideals and principles that are our common heritage, and thus the very moral foundations of society. " Doping states Štablová and Brejcha (2006) as "Doping is the use of substances that belong to the group of prohibited means, but also the use of illegal methods such as e.g. blood doping." However, both definitions lack the motivation and purpose of the use of illicit substances. Kuklík et al. (2012) offers a much broader clarification of the concept. It is any attempt by an athlete or other person (manager, coach, doctor, physiotherapist, masseur) to increase mental performance, or to treat an illness, injury - unless medically justified, only for the purpose of competition. "This includes the use, administration or prescribing of prohibited substances before or during a competition." He further emphasizes that this also applies to out-of-competition testing of anabolic steroids, peptide hormones and related substances with similar effects. Other prohibited methods or manipulations of samples taken for testing are also considered doping. Kuklík et al. (2012) also consider the incompleteness of the above definition in the context of constantly evolving modern technologies, i.e. whether it includes all possible doping methods. It leaves this question of creating a new definition open... Nowdays, we can declaredly say that the issue of doping concerns not only athletes, but has also been noted in professions that require physical strength, fitness and mental resilience to stress.

The International Federation of Sports Medicine gave attention to the problem of doping in sports as early as the 1920s, and in 1928, doping was banned at a meeting of the International Olympic Committee at its meeting. It was not until the 1960s that the first list of banned substances were adopted, but also without any sanctions. In 1967, the International Olympic Committee introduced anti-doping controls for the Olympic Games in Mexico, and in 1968 it defined the term doping (Štáblová, Brejcha et al., 2006). At the Montreal Olympics, doping controls on anabolic steroids have already been systematically carried out. In the early 1990s, it was known that banned substances and methods were used in at least forty types of disciplines, especially in elite sports. Their number already exceeded more than hundreds. In response, a list of banned substances and methods was issued, which was an effort to coordinate the efforts of international and domestic sports federations, sports organizations and sports organizations, and prevent their use from the public. During this period, a list of doping substances and methods was compiled annually and systematically by the Medical Committee of the International Olympic Committee and was one of the annexes to the International Olympic Charter against Doping in Sport (by adopting it we can speak of a systematic fight against doping). It was binding for all sports associations of the member countries. Gradually, the control system was overhauled, but despite any activity, doping came to the forefront of sports activities, which resulted in many sports scandals. Let's move on a little further, to the 21st century.

The World Anti-Doping Agency (WADA, Montreal, Quebec, Canada) first issued the World Anti-Doping Code in 2003, which entered into force in 2004. It was amended on January 1, 2009. Further

revisions were approved by the World Anti-Doping Council. Anti-Doping Agency in Johannesburg on 15 November 2013. The Comprehensive Revised Code is effective from 1 January 2015. Its primary objective is to protect the fundamental rights of athletes to practice sport without doping, to promote health, justice, equality for athletes, but also to harmonize, coordinate and implement anti-doping programs at international and national level to combat doping, detect, discourage and prevent doping (World Anti-Doping Agency – *Svetový antidopingový kódex 2015*, 2015).

Doping is defined by the Anti-Doping Agency of the Slovak Republic as the occurrence of one or more anti-doping rule violations in the following cases: evidence of the presence of the prohibited substance or its metabolites, markers, the use or attempted use of a prohibited substance or prohibited method by an athlete, avoidance, refusal or non-sampling, failure to provide information on whereabouts, falsification or attempted falsification during any part of a doping control, possession of a prohibited substance or prohibited method, trafficking in, or attempting to trade in, any prohibited substance or prohibited method, the submission or attempted administration of any prohibited substance or prohibited method to any athlete during the competition, or the submission or attempted administration of any prohibited substance or prohibited method that is prohibited outside the competition to any athlete outside the competition, participation, prohibited association (Antidoping Agency SR - *Antidopingové pravidlá SR. Verzia 1.2. 2017.*, 2017).

SUBSTANCES WITH HORMONAL AND BIOLOGICAL EFFECTS

Steroid hormones are a large group of compounds with a perhydrocyclopentanephenanthrene nucleus and are divided into glucocorticoids, mineralocorticoids, androgens, estrogens and progestogens according to their biological effect.

In general, anabolics are considered to be substances (anabolic substances) that promote anabolism, which consists in the creation of more complex molecules and the storage of energy in the supply. These include protein synthesis, the formation of glycogen stores or the energy of proteins and fats.

Natural anabolic substances are androgens, i.e. male sex hormones produced by the testes, which are responsible for the development of primary and secondary male sexual characteristics, spermatogenesis and stimulation of muscle growth (Chromý, 2008).

Androgenic anabolic steroids were developed in the 1930s to treat hypogonadism (a disorder of the gonads). Today, they are mainly used to treat delayed puberty and diseases associated with the weakening of the body. From a medical point of view, these are synthetic derivatives of the hormone testosterone.

They support muscle growth (anabolic effect) and the development of male sexual characteristics (androgenic effect). Anabolic steroids are among the substances that are abused mainly to increase sports performance, increase muscle weight, and increase strength. They are abused especially in sports where it is necessary to use a lot of force or in endurance disciplines. They are also used for regeneration after physically demanding training. They found their place in bodybuilding, fitness. This is a society-wide problem, in which we can also include drug use. The most risky group are adolescents, who often reach for the mentioned substances, which significantly affect their physical and mental health. As they affect the growth of skeletal muscles, they were abused mainly by bodybuilders, weightlifters and later they got into other sports. Their use logically led to influencing the results in sports activities. Many manufacturers intentionally chemically modify these substances in order to maximize their anabolic effects and suppress their androgenic effect. They are also risky

because of to the emergence of a specific form of addiction during their long-term use (Šimurka & Zavřel, 2008). Effective combating their production, distribution and use is currently an important element in combating crime in this area (health damage, addiction).

Anabolic steroids are among the most frequently detected chemicals in sports doping controls. They are responsible for proteosynthesis, which results in a positive nitrogen balance in the body, it is the so-called anabolic effect. Their advantage is that they shorten the part for regeneration and reduce the proportion of body fat. Their downside is that they affect male sexual characteristics. In English-speaking countries, the terms "juice", "steroids", "grain" have been used for anabolic steroids, and the term "roids" is used in American English (Chromý, 2008).

Chaloupková et al. (2019) states in its publication that according to an anonymous internet questionnaire (Parkinson & Evans, 2006) from 2006, almost 100% of users of anabolic steroids administer intramuscularly. 89% of users obtain them from illegal sources and more than 50% admit that they use steroids synthesized in illegal laboratories. Subjective side effects occur in almost 100% of anabolic steroids users. In addition, testosterone and its derivatives can be administered in the form of tablets, by injection, transdermally, through the nasal mucosa, the mucosa of the eye, rectally. They are used in low doses, because a significant increase in muscle mass can negatively affect sports performance.

DIVISION OF SUBSTANCES WITH HORMONAL AND BIOLOGICAL EFFECTS

Nowadays, the World Anti-Doping Agency (2020) distributes prohibited substances for the purposes of doping in sport and subsequently also the Antidoping Agency of the Slovak Republic (Antidoping Agency SR – *Zoznam zakázaných látok a metód*, 2020) as follows (we present a simplified form for publication purposes):

S0. Non - phase - in substances

S1. Anabolic substances

- Subgroup S1.1 Anabolic androgenic steroids
- Subgroup S1.2 Other anabolic substances

S2. Peptide hormones, growth factors, related substances and mimetics

- Subgroup S2.1 Erythropoietins and substances affecting erythropoiesis
- Subgroup S2.2 Peptide hormones and their release factors
- Subgroup S2.3 Growth factors and their modulators

S3. Beta-2 agonists

S4. Hormonal modulators and metabolic modulators

- Subgroup S4.1 Hormonal modulators
- Subgroup S4.2 Metabolic modulators

S5. Diuretics and masking agents

MISUSAGE OF SUBSTANCES WITH HORMONAL AND BIOLOGICAL EFFECTS

In the second part of our paper we will not speak about the first group of substances, i.e. exogenous and endogenous anabolic androgenic steroids, but rather we will list several selected substances with different hormonal and biological effects that are abused in sports doping.

To group S0. Non-phase-in substances include pharmacological substances that do not fall into any of the above groups and are not approved by a public authority for therapeutic usage in humans, as well as substances in preclinical, clinical or discontinued testing, synthetic drug derivatives and veterinary-approved medicinal products.

Other anabolic substances such as Clenbuterol, selective androgen receptor modulators, tibolone, zeranol, zilpaterol are included in subgroup S1.2. Selective androgen receptor modulators (SARMs) are substances that have a similar effect as anabolic androgenic steroids and do not even have a characteristic steroid structure. However, they have a 10-fold greater affinity for androgen receptors than testosterone alone, and once bound to the appropriate receptors, it is not possible for them to bind to testosterone. Currently, **ostarin** and **andrarine (S-4)** are the best studied. These are substances that can be taken orally and were originally used to treat muscular dystrophy, osteoporosis and benign prostatic hyperplasia. The products are illegally manufactured in China and distributed in Europe and America. As an example, we present a positive out-of-competition doping finding of ostarin in cyclist Nikita Novikov (May, 2013) and in the American wrestler Obenson Blanc (June, 2013), for whom they were imposed a two-year ban on sports activities. In June 2013, a positive doping finding for andarin was found in the Jamaican horse Damar Robinson, who was punished by a one-year ban (Antidoping Agency SR - *Anabolika*, 2020).

Another hazardous group that includes banned substances is S2. Peptide hormones, growth factors, related substances and mimetics. These are substances with a diverse chemical structure and a wide range of effects. In general, these are proteins that are naturally formed in the human body and have stimulatory effects that affect the production of other substances.

The authors Pagáč, Gulán and Csáderová (2018) point out the abuse of erythropoietin (EPO) and other substances that affect erythropoiesis. Examples include erythropoietin receptor agonists, hypoxia-induced factor stabilizers, GATA inhibitors, and others. **Erythropoietin** is a glycoprotein cytokine that is excreted by the kidneys in cellular hypoxia. Its main function is to stimulate the production of red blood cells in the bone marrow. It was artificially manufactured in the 1980s to treat anemia. It is abused mainly for its ability to improve the endurance of the athlete and reduce the time needed to regenerate the human body. In 1998, the Festina team was expelled from the Tour de France for the use of erythropoietin because everyone had systematically used this banned doping substance. In 2013, Lance Armstrong also confessed to doping, i.e. he took erythropoietin, growth hormones, testosterone and cortisone along with blood transfusions. There are also cases of this form of doping in cross-country skiing, biathlon, triathlon, marathon running, speed skating, boxing, and weightlifting. Negative effects include increased hematocrit, increased blood pressure, risk of thrombosis, heart attack, and stroke.

In this group of substances, we must also mention **growth hormone** itself. Human growth hormone (hGH) consists of 191 amino acids and is often referred to as somatotropin. It has anabolic effects and therefore causes the growth of muscle mass. Skier Andrus Veerpalu or British rugby player Terry Newton (Antidoping Agency SR - *S2. Rastový hormón*, 2020) was convicted of its use.

To group S3. Beta-2 agonists include selective beta-2 agonists and non-selective beta-2 agonists, including any optical isomers. Examples include fenoterol, formoterol, higenamine, indacaterol, olodaterol, prokaterol, reproterol, salbutamol (with certain exceptions), salmeterol (with certain exceptions), terbutaline, tretoquinol, tulobuterol, Vilanterol. These substances are most often used for airway dilation in the treatment of asthma. These substances are abused by athletes for their ability to stimulate proteosynthesis (anabolic effect) and burn fat in high doses.

We can also include the above-mentioned **clenbuterol** in this group, which, although it belongs to the group S1.2 other anabolic substances, belongs to among beta-2 agonists due to its characteristic structure. Clenbuterol is known as a substance which was given to animals for significant fattening and the consumption of such foods can lead to positive doping findings in athletes. If an athlete has to undergo asthma treatment with beta-2 agonists, a therapeutic exemption must be granted. However, if an athlete experiences a beta-2 agonist with a diuretic or masking agent, this is considered an unfavorable analytical finding (unless a therapeutic exemption has been established for these agents). The Anti-Doping Agency SR states that in 2018 beta-2 agonists were detected in samples of athletes 164 ×, which is 4% of all adverse analytical findings (Antidoping Agency SR – *Higenamín ako zakázaný beta-2 agonista*, 2020).

To group S3. Beta-2 agonists also include the substance **higenamine**, which is found in several Asian plants such as *Nelumbo nucifera*, *Aconitum carmichaelli* or *Nandina domestica* used for culinary purposes. Higenamine can stimulate the relaxation of bronchial smooth muscle, which leads to dilation of the airways and at the same time increase the heart rate and myocardial contractility. It is most often used as a nutritional supplement for weight loss and a means to increase sports performance. It is legally sold in Europe, the USA and Canada (*https://www.a1supplements.com/swft-stims-higenamine*).

Beta-2 agonists are most often abused in endurance sports (cycling, athletics, swimming, cross-country skiing), where an increased supply of oxygen is needed. However, it should be emphasized that in athletes who do not suffer from asthma, these substances tend to have negative effects. Negative effects on the human body include excessive sweating, restlessness, tremor, tachycardia, angina pectoris, decreased blood potassium levels, arrhythmias, increased glucose levels. Here are some examples of illicit doping substance abuse: in 2010, clenbuterol was detected in a urine sample by Spanish cyclist Albert Contador. His victory in the Tour de France was unpaid and he was banned from working for two years. Austrian bodybulider Andreas Münzer died at the age of 31 of organ failure due to the use of beta-2 agonists. In 2002, Belgian police found erythropoietin, morin and Clenbuterol in the house of cyclist Frank Vandenbroucke. In February 2019, the sports activity of the Polish hockey player Lukasz Bartak was suspended for 18 months due to a positive finding of higenamine. The Anti-Doping Agency of the Slovak Republic states that in 2018 higenamine was detected worldwide in 42 samples of athletes, which is 26% within the group of beta-2 agonists (Antidoping Agency SR – *Higenamín ako beta-2 agonista*, 2020).

DOPING IN SLOVAK REALITIES

Since the task of every advanced society is to protect its own public health, the Slovak legal system also regulates the use of substances with hormonal effects by a criminal law, for example in Slovak Act no. 300/2005 Coll. The Criminal Code (§ 176), whose task is to prevent the access and use of these substances (including doping methods) by individuals. The wording of the offense with the legal name is as follows: "Unauthorized treatment of substances with an anabolic or other hormonal effect". The

purpose of this rule of law is, in essence, to prevent the unauthorized manufacturing, importing, exporting, transporting, offering substances with hormonal effects on a larger scale or providing, administering anabolic androgenic steroids or other substances with a hormonal effect to another person for a purpose other than treatment. In this case, intermediary activity is also punished. The penalty rate ranges from three years to 15 years, depending on the seriousness of the offender's conduct. It should be emphasized that this is not just a single provision of the Criminal Code.

In connection with the above-mentioned criminal offense (Section 176 of the Criminal Code), we consider it necessary to emphasize that by analyzing data from the Evidence-Statistical Crime System, we find that in 2015 no single criminal offense was registered in this system according to the above paragraph. In 2016, two cases were identified. In 2017, 10 violations were detected, two cases were clarified and three persons were prosecuted for this crime. In 2018, 5 violations of the law were detected, one case was clarified, while the damage of 134 euros caused by this crime was also registered, and in 2019, 5 cases were detected, one of which was subsequently clarified. From this simple calculation, we can conclude that the detection and clarification of crime in connection with the abuse of anabolic androgenic steroids and other substances with hormonal effects is at a very low level, which is in contrast to the general knowledge on this issue. From the analyzed data we can conclude that the abuse of these substances, which significantly damage the health of the human body has a high latency and in our opinion, it is not given sufficient attention, as is the case with drug crime. Another argument in relation to the low number of detected cases of substances with hormonal effects abuse may be that in detecting and clarifying drug and pharmaceutical crime, anabolic androgenic steroids and other substances with hormonal effects abuse is only an associated problem occurring in an insignificant form and is qualified by other criminal offenses.

CONCLUSION

In the introduction to our paper, we analyzed the historical context of the use of doping substances, and we found that these substances, which support the activity of the body through various subjective manifestations at the physiological or mental level, have been used since time immemorial. Likewise, the development of the word "doping" itself has its historical framework, which we have also described. Since the use of prohibited doping substances before, after or during sports activities at the national or global level, resp. their abuse by professional or amateur athletes is perceived in society as a negative phenomenon, so we have included in the contribution an international and national attitude to this negative phenomenon. The aim of our paper is not a simple definition of substances with hormonal and biological effects, their medical use, division, calculation of their huge amount, but we want to point out their abuse by young people (age limit is decreasing), people who are sensitive to their sports ideals and athletes (top or amateur).

We presented the reader with a wide range of chemicals – substances with hormonal effects. This is only an illustrative calculation, because there are many more substances included in the list of banned substances than we stated in our contribution. The Anti-Doping Agency of the Slovak Republic regularly prepares information a list not only about prohibited substances and methods, but also about authorized drugs, which are classified into groups according to the disease for which they are to be used and which can be used by the athlete (Antidoping Agency SR - *Povolené lieky 2019*, 2019). In this context, we want to draw attention not only to the abuse of substances with hormonal effects, respectively all prohibited doping substances and nutritional supplements during sports activities, but also on the issue of pharmaceutical crime, which also addresses the issue of combating illegally

manufactured pharmaceuticals, which can also be reached by top athletes. In this context, we still share Drugda's view (2019) that pharmaceutical crime has a negative impact on society as a whole in terms of public health threats through the production of counterfeit medicines, drugs, nutritional supplements, medical devices in underdeveloped countries with their subsequent smuggling, illegal distribution, and sales to more developed countries of the world. It further points out that those pharmaceutical products can be sold online or through individuals, and that this issue therefore needs to be addressed as a matter of urgency.

In the article, we also clearly indicated the forms of abuse and we also presented a huge calculation of the negative effects of substances with hormonal and biological effects on the human body. It is the negative effects of these often readily available hazardous substances that are a major problem for the public health of our society.

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