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The World Anti-Doping Code: Truths and Wrongs

Dünya Antidoping Şifresi: Doğrular ve Yanlışlar

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ABSTRACT

World Anti Doping Agency (WADA) is the unique authority to set the rules of doping and banned substances all around the World and the prohibited list is annually updated. It aims to prevent the use of the compounds that may increase athletic performance, hence create a fair and equal status for all competitors and also protect athlete's health from the unexpected or side effects of the compounds that have a potential for misuse. The list of 2018 consists three major titles of prohibited substances and methods. Prohibited substances are classified as "S" code, whereas prohibited methods as "M" and substances prohibited in particular sports as "P." The present review criticize some illogical parts of the 2018 prohibited list. For example; despite the most of the beta-2 agonists, diuretics/masking agents and stimulants were banned, a few of them are not accepted as doping in the use of limited doses. Some compounds that have a serious potential to increase mood and physical resistance similar to amphetamines, such as MAO inhibitors and anticholinergics have not been banned yet by WADA. Also the prohibition/allowance of beta blockers and alcohol in some sports were criticized in the present paper.

Keywords: Doping, pharmacology, WADA, prohibited, olympics

ÖZ

Dünya Anti Doping Ajansı (WADA), doping ve yasaklı maddeler konusunda Dünya'daki kuralları belirleyen tek otorite olup, yasaklı maddeleri içeren listesini her yıl güncellemektedir. Buradaki amaç, atletik performans artışı yapan maddelerin kullanımını önlemek ve böylece tüm yarışmacılara eşit ve adil bir ortam yaratmak yanında, kötüye kullanım potansiyeli taşıyan bu maddelerin sebep olabileceği beklenmeyen ve istenmeyen etkilerinden sporcuları korumaktır. 2018 yasaklı maddeler ve metodlar listesi üç alt başlıktan oluşmaktadır. Yasaklı maddeler "S" kodu ile sınıflandırılmışken, yasaklı metodlar "M", bazı özel spor branşlarındaki yasaklılar ise "P" ile sınıflandırılmıştır. Bu derlemede WADA 2018 yasaklılar listesindeki mantıksız uygulama ve talimatlar eleştirilmektedir. Örneğin; birçok beta-2 agonist, diüretik/maskeleyici ajanlar ve uyarıcı maddeler yasaklanmış olmasına ragmen, bu gruplardan az sayıda maddenin limitli kullanımına izin verilmektedir. MAO inhibitörleri ve antikolinerjikler gibi, amfetamin benzeri şekilde ruhsal durumu yükselten ve fiziksel dayanıklılığı arttıran maddeler WADA tarafından henüz yasaklanmamıştır. Ayrıca beta blokerler ve alkolün bazı branşlarda serbest, bazılarında ise yasaklı olması da tartışılmıştır.

Anahtar sözcükler: Doping, farmakoloji, WADA, yasaklı, olimpiyat

Introduction

Since ancient times, competitive athletes have been familiar with the use of ergogenic aids, and they will probably continue to use unfair and harmful substances in future because their inclination to victory, along with the mirage of glory and money, will probably overcome health and legal risks. Nowadays, new drugs and substances that are not currently banned by World Anti-Doping Agency (WADA), with ergogenic or masking potential are quickly adopted, driven by a desire to win and the necessity of avoiding detection. Such compounds and methods that were discussed in our previous report (1) are followed by WADA, and the prohibited list is annually updated. The Prohibited List of 2017 has recently been released on their website. First, it aims to prevent the use of the compounds that may increase athletic performance, hence create a fair and equal status for all competitors. Second, it is targeting to protect athlete's health from the unexpected or side effects of the compounds that have a potential for misuse. On the other hand, athletes may have illnesses or conditions that require them to take particular medications under the Prohibited List, and a Therapeutic Use Exemption (TUE) may give an athlete the authorization to take the needed medicine.

The list of 2018 consists of three major titles of prohibited substances and methods. Prohibited substances are classified as "S" code, whereas prohibited methods as "M" and substances prohibited in particular sports as "P." Despite the fact that

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WADA reviews the international standards of the prohibited list (IS), some minor changes have been spotted by the sports professionals all around the World.

Prohibited Substances

The S1 subtitle prohibits anabolic agent's use, while S2 is about peptide hormones, growth factors, related substances, and their mimetics. Under the S3 subtitle, the use of all beta-2 agonists including all optical isomers was prohibited. Everything seems sensible till now, but illogical exceptions have started by that point until the same subtitles of S3, with the exceptions of the following:

- Inhaled salbutamol (maximum 1600 micrograms over 24 hours, should not exceed 800 micrograms over 12 hours starting from any dose);
- Inhaled formoterol (maximum delivered dose, 54 micrograms over 24 hours); and
- Inhaled salmeterol: (maximum 200 micrograms over 24 hours; it was expressed in the 2016 prohibited list of WADA such as "Inhaled salmeterol in accordance with the manufacturer's recommended therapeutic regimen"). The presence of salbutamol in urine in excess of 1000 ng/mL or formoterol in excess of 40 ng/mL is not consistent with therapeutic use of the substance and will be considered as an Adverse Analytical Finding (AAF) unless an athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use a therapeutic dose (by inhalation) up to the maximum dose indicated above."

Beta-2 agonists are the mainstay of pharmacotherapy in chronic obstructive pulmonary disease and another respiratory distress status. The short-acting beta-2 agonists, including salbutamol and fenoterol, have a rapid onset of action, i.e., bronchodilating effect for 3-6 hours. The long-acting beta-2 agonists, including salmeterol and formoterol, have a 12-hour action (2). It was reported that beta-2 agonists improve forced expiration volume but also increase mean oxygen consumption, hence decreasing athletic economy (3). Similar to this, there are mostly negative reports on beta-2 agonists on improving athletic performance (4, 5). On the other hand, there are some positive reports on beta-2 agonists that improve athletic performance (6, 7) and that beta-2 agonists improve some parameters but not all of the athletic performance (8, 9). Ahead of the controversy reports in the literature, allowing the limited use of beta-2 agonists by WADA has to be discussed in that part of the article. First, salbutamol, formoterol, and salmeterol are allowed to be used in limited doses, whereas other beta-2 mimetics such as albuterol, bitolterol, levalbuterol, pirbuterol and terbutaline, are not. The very important question is why. Second, allowed beta-2 mimetics use in limits has to be administered by inhalation in accordance to WADA 2018 international standard's guide. It is not possible to determine the routes of administration of those molecules by urine or blood sample analysis. In certain cases, WADA has to explain how to determine the administration route of such compounds. Third, in the group of limitedly allowed molecules of beta-2 agonists, maximum doses for 24 hours and limits of the urine levels of salbutamol and formoterol were determined, whereas for salmeterol, there is no indication for urine or blood sample's level. Fourth, there is no action for determining an athlete's pharmacogenetic profile for metabolizer enzymes of salbutamol and formoterol, such as SULT1A3 (10), ADCY9, and ADRB2 (11). If an athlete's genotype for these enzymes was known by somebody, it would get them a very obvious advantage in competitions, and the limitations on beta-2 mimetics by WADA become useless. Fifth, under the S3 subtitle, it was stated that "The presence in urine of salbutamol in excess of 1000 ng/mL or formoterol in excess of 40 ng/mL is not consistent with therapeutic use of the substance and will be considered as an AAF unless the athlete proves, through a controlled pharmacokinetic study." This statement may lead to misuse of any substances by the authorities. Including elite athletes in the pharmacokinetic studies will be very moot, e.g., before international competitions, some local authorities may lead to including athletes in a pharmacokinetic study and use of supratherapeutic doses of salbutamol and/or formoterol, unless be blamed to misuse by WADA. Lastly, if TUE allows that athlete the authorization to take the needed medicine, why are those limitations and rules for administering beta-2 agonists necessary?

The S5 subtitle is about the use of diuretics and masking agents. In this chapter, most of them were seems prohibited, except drospirenone and pamabrom. Drospirenone is well-known and widely used in combination mostly with estrogen for oral contraception (12), premenstrual syndrome (13), polycystic ovary syndrome (14), etc. It is used obviously for the benefits of its diuretic effect. Conversely, pamabrom is not well-known and not a widely prescribed drug in clinics. It is used to cease pain in dysmenorrhea primarily, in combination with paracetamol (15). It is not clear that why so rarely used compounds were allowed to use while most others were prohibited by WADA.

Prohibited Methods

Prohibited methods were coded as "M" and under the M1 subtitle of "manipulation of blood and blood components," banned methods and substances were described. In this chapter, administering supplemental oxygen by inhalation could be used during training periods and competition. Supplemental oxygen provided during recovery periods of the interval-based exercise was found to improve recovery time of the pulse oximetry (16). It was also reported that supplemental oxygen flows during exercise, arterial pO2 levels increase, and blood pH increases significantly after terminating administration of hyperoxic air (17). On the other hand, there are some negative reports on supplemental oxygen's benefits during exercise (18). Overall, it will be an unpleasant scene to witness an athlete inhaling supplemental oxygen during competitions. Under the "M2-chemical and physical manipulation" subtitle, intravenous infusions and/or injections of more than

a 100 mL per 12 hours, were prohibited. Actually, it is impossible to detect the exact volume of injections in a certain time period using modern technology.

Substances, Methods, Prohibited in-Competition

The S6 subtitle describes prohibited stimulants with some exceptions. In this list, clonidine, bupropion, caffeine, nicotine, phenylephrine, phenylpropanolamine, pipradol, and synephrine were included in the 2018 Monitoring Program and were not considered as prohibited substances. On the other hand, pseudoephedrine is prohibited when its concentration in urine is >150 micrograms per milliliter, and its active metabolite cathine is prohibited when its concentration in urine is >5 micrograms per milliliter. Also, ephedrine and methylephedrine are prohibited when its concentration in urine is >10 micrograms per milliliter. The ergogenic effects of stimulants such as ephedrine, including increased energy, time to exhaustion, power output, running speed, and weight loss, were previously reported (19). Pseudoephedrine was reported to increase 1,500-m runner's performance at a dose of 2.5 milligram per kilogram (20). In another study, it was proven that 180 milligram pseudoephedrine taken 60 minutes before the onset of high-intensity exercise improved cycling time-trial performance in well-trained cyclists (21). Stimulants were reported to provide an unfair advantage; increased alertness, diminished fatigue, and cardiovascular activation can be advantageous in many sport events (22). On the other hand, a meta-analysis found insufficient evidence to support a performance benefit from dose-dependently administered ephedrine (23) and pseudoephedrine (20). According to the accumulated data, for both compound's serious side effects primarily involve the cardiovascular and central nervous systems, and due to the genetic variations on metabolizing enzyme levels, probability the occurrence of any side effects becomes independent of the dose for both drugs. So it is not understandable that the dose or biological sample limits of pseudoephedrine and ephedrine levels. In case of life-threatening clinical indications and necessities of them, they will be administered under the rules of TUE.

Administering both compounds in non-life-threatening indications for symptomatic benefits, such as influenza infection, is not crucial with the existence of many other alternative drug combinations. Therefore, such compounds have to be classified as prohibited or not prohibited substances without dose limitation by WADA. Additionally, MAO inhibitors, such as clorgiline, phenelzine, moclobemide and tranylcypromine, which are used to treat depression, and anticholinergics, such as scopolamine, biperidene, trihexyphenydil and benztropine, have some serious potential to increase mood and physical resistance, very similar to amphetamines. Both groups have not been yet banned by WADA.

In the previous bulletin of 2017; the P1 subtitle consisted alcohol prohibition in competitions only in particular sports including Air Sports (FAI), Archery (WA), Automobile (FIA) and Powerboating (UIM) only. It was very surprising that, during the competitions of Motorcycle sports (FIM), alcohol consumption was not banned. In 2018 prohibited list of WADA, alcohol was removed from the list.

Under the P2 beta blockers subtitle, it was described the prohibition of the use of beta-blocker compounds in competition in automobile sports, billiards, darts, golf, skiing, and underwater sports. Also, in archery (WA) and shooting (ISSF and IPC) sports, the beta blockers are prohibited in and out of the competitions. Beta blockers were used to prevent social stress symptoms, such as stress-induced tremors, before competitions by athletes. Despite their prohibition in and out of the competitions are correct, WADA must explain why other sports were not included in the prohibition list, especially gymnastics and fencing.

Conclusion

The doping issue should be individualized to each athlete. Clinical pharmacology can serve to identify drug-drug interactions, and organ function alterations, age, sex, lifestyle aspects such as exercise, sleep durations, and pharmacogenetics can alter drug response. Unfortunately, we do not yet have validated biomarkers for "true love," and it has the same success criteria as the Olympics. With WADA's important contribution to the detection, diagnosis, and monitoring of doping, efforts can be considered far more likely to define and sustain "play true."

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