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Title: The World Anti-Doping Code: Truths and Wrongs

Running Head: The World Anti-Doping Code

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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 which was discussed in our previous report (1), are followed by WADA and prohibited list is updated annually. Prohibited list of 2017 has been released in their web site, recently. First of all, it aimes to prevent the use of the compounds that may increase the athletic performance, hence to create a fair and equal status for all competitors. Second, it is targeting to protect athlete's health from unexpected or side effects of the compounds which have a potential to misuse. On the other hand, athletes may have illnesses or conditions that require them to take particular medications under the Prohibited List, a Therapeutic Use Exemption (TUE) may give that athlete the authorization to take the needed medicine.

The list of 2017 consists 3 major titles of prohibited substances and methods. Prohibited substances classified as "S" code, while prohibited methods as "M" and substances prohibited in particular sports as "P". Despite WADA rewievs the international standards of prohibited list (IS) annually, some minor changes have been spotted by the sport professionals all around the World.

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Prohibited substances

The S1 subtitle prohibits anabolic agents use, while S2 is abouth peptide hormones, growth factors, related substances and mimetics of them. Under the subtitle of S3, the use of all beta-2 agonists including all optical isomers were prohibited. Everything seems sensible by now, but illogical exceptions have started by that point under the same subtitles of S3, with the expression of;

"Except:

• Inhaled salbutamol (maximum 1600 micrograms over 24 hours, not to exceed 800 micrograms every 12 hours);

• Inhaled formoterol (maximum delivered dose 54 micrograms over 24 hours); and

• Inhaled salmeterol: maximum 200 micrograms over 24 hours (It was expressed in 2016 prohibited list of WADA such as; "Inhaled salmeterol in accordance with the manufacturer's recommended therapeutic regimen"). The presence in urine of salbutamol in excess of 1000 ng/mL or formoterol in excess of 40 ng/mL is presumed not to be an intended therapeutic use of the substance and will be considered as an Adverse Analytical Finding (AAF) unless the Athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of the therapeutic inhaled dose up to the maximum dose indicated above". Beta-2 agonists are the mainstay of pharmacotherapy in chronic obstructive pulmonary disease and other respiratory distress status. The short-acting beta-2 agonists, including salbutamol, and fenoterol, have a rapid onset of action, bronchodilating effect for 3-6 hours. The long-acting beta-2 agonists, including salmeterol and formoterol, have 12-hours duration of action (2). It was reported that beta-2 agonists improve forced expiration volume but also increase mean oxygen consumption and hence decreases athletic economy (3). Similar to that, there are mostly negative reports of beta-2 agonists on the improving athletic performance (4,5). On the other hand, there are some positive reports of beta-2 agonists which improve athletic performance (6,7) and some reports on that beta-2 agonists improve some parameters but not all of athletic performance (8,9).

Ahead of that controversy reports in the literature, allowing to 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 use in limited doses, while other beta-2 mimetics such as albuterol, bitolterol, levalbuterol, pirbuterol and terbutalin, are not. The very important question is; why? Second, allowed beta-2 mimetics use in limits, have to be administered by inhalation in according to WADA 2017 international standard's guide. It is not possible to determine the routes of administration of that molecules, by urine or blood sample analyses. In certain case, 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, while for salmeterol, there is no indication for urine or blood sample's level. Fourth; there is no action for determining the athletes pharmacogenetic profile for metabolizer enzymes of salbutamol and formoterol, such as SULT1A3 (10), ADCY9 and ADRB2 (11). If an athlete's genotype for those enzymes was known by somebody, it would get them a very obvious advantage in competitions and the limitations for beta-2 mimetics by WADA, become illogical. 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 presumed not to be an intended therapeutic use of the substance and will be considered as an Adverse Analytical Finding (AAF) unless the Athlete proves, through a controlled pharmacokinetic study.". That statement may lead to misuse of any substances by the authorities. Including elite athletes to the pharmacokinetic studies, will be very moot. For example; beforehand the international competitions, some local authorities may lead to include the athletes in a pharmacokinetic study and the use of supratherapeutic doses of salbutamol and/or formoterol, unless be blamed to misuse by WADA. Sixth; if Therapeutic Use Exemption (TUE) allow to cure 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 that chapter, most of them were seems prohibited, except drospirenone and pamabrom. Drospirenone is a well known and widely use in combination mostly with estrogene for oral contraception (12), premenstruel syndrome (13), polycystic ovary syndrome (14), etc. It uses obviously for the benefits of it's diurethic effect. Controversy to

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drospirenone, pamabrom is not a 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 diuretic compound was 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 that chapter, administering supplemental oxygen by inhalation was allowed to use during the training periods and competition. Supplemental oxygen provided during the recovery periods of interval based exercise was found to improve the recovery time of pulse oximetry (16). It was also reported that; supplemental oxygen flows during exercise, arterial pO2 levels were found to increase and blood pH increased significantly after terminating administration of hyperoxic air (17). On the other hand, there are some negative reports on supplemental oxygen's benefits during the exercise (18). Further of all, it will be very unpleasant scene for the witness that an athlete is inhaling supplemental oxygen during the competition. Under the "M2-chemical and physical manipulation" subtitle, intravenous infusions and/or injections of more than 50 mL per 6 hour, were prohibited. Actually it is impossible to detect the certain volume of injections in a certain time period, by using modern technology.

Substances & Methods, Prohibited *in-competition*

S6 subtitle describes prohibited stimulants by some exceptions. In that list, clonidine, bupropion, caffeine, nicotine, phenylephrine, phenylpropanolamine, pipradol and synephrine were included in the 2017 Monitoring Program and were not considered as prohibited substances. On the other hand, pseudoephedrine prohibited when its concentration in urine is greater than 150 micrograms per mililiter, and it's active metabolite cathine, prohibited when its concentration in urine is greater than 5

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micrograms per mililiter. Also, ephedrine and methylephedrine, prohibited when the concentration of either in urine is greater than 10 micrograms per mililiter. The ergogenic effects of stimulants such as ephedrine, including increased energy, time to exhaustion, power output, running speed, and weight loss were reported in the past (19). Pseudoephedrine was reported to increase 1500 m runners performance at a dose of 2,5 mg/kg (20). In another study, it was proven that 180 mg of pseudoephedrine, 60 min 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 fatique 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 with ephedrine (23), and pseudoephedrine, dose dependently (20). In according to accumulated data for both compound's serious side effects, primarily involve the cardiovascular and central nervous systems, and due to the genetic variations of metabolizing enzyme levels, probability the occurence of any side effects becomes independent of dose for both drugs. So it doesn't seem sensible for the dose or biological sample limitations of pseudoephedrine and ephedrine levels. In case of life threating clinical indications and necessities of them, they will be administered under the rules of Therapeutic Use Exemption. Administering both compound in non-life threating indications for symptomatic benefits, such as influenza infection is not crucial with many other alternative drug combination existence. So, such compounds have to be classified as prohibited or not prohibited substances without dose limitation, by WADA.

The P1 subtitle describes alcohol prohibiton in competition only in particular sports including Air Sports (FAI), Archery (WA), Automobile (FIA) and Powerboating (UIM) only. It is very surprising that, during all of the automobile sports competition, alcohol is prohibited while Motorcycle Sports (FIM) are not. So, it is allowed to be drunk while riding motorcycle in competitions.

P2 beta blockers subtitle describes the prohibition the use of beta blocker compounds in competition in automobile sports, billiards, dart, golf, skiing and underwater sports. Also in archery (WA) and Shooting (ISSF, IPC) sports, beta blockers are prohibited in and out of the competitions. Beta blockers were administered to prevent social stres symptoms; such as stres induced tremors, beforehand the competitions by athletes. Despite the prohibition of them in and out of the competitions are correct,

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WADA must explain why other sports were not included the prohibition list, especially gymnastic and fencing.

Conclusion

The doping issue should be individualized to each sportsman. Clinical pharmacology can serve to identify as drug-drug interactions, 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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