The Athlete Biological Passport: an integral element of innovative strategies in antidoping

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ABSTRACT
Concern for the health of athletes and integrity of sport resulted in the banning of specific substances although many years passed before analytical testing took place. Soon doping control programmes became synonymous with urine tests and adverse analytical findings. This system has its limits due to the detection window of prohibited substances, the timing of sample collections and the sophistication of some doping regimens. There have been a number of situations where these limits were demonstrated by athletes who proclaimed innocence based on passing their analytical tests only to later confess to doping. New strategies were called for to protect clean athletes. In the current World Anti-Doping Code, there are eight means to an Anti-Doping Rule Violation (ADRV). Article 2.2 states that the use of a prohibited substance may be established by any reliable means including witness statements, documentary evidence or evaluations of longitudinal profiling. In 2006, the World Anti-Doping Agency (WADA) with the support of some International Federations (IFs) gathered a group of experts to develop a harmonised programme on longitudinal profiling, or serial analysis of indirect biomarkers of doping, that was both scientifically and legally robust. This culminated in the WADA Athlete Biological Passport (ABP) Operating Guidelines and Technical Documents, published in 2009. The ABP is a paradigm that infers the use of prohibited substance (or method) by the monitoring of discriminant biomarkers over time. The haematological module detects blood manipulation by the use of erythropoietic stimulating agents or via blood transfusions. The steroidal module aims to identify endogenous anabolic androgenic steroids when administered exogenously and other indirect steroid doping substances or methods. Other ABP modules (endocrine, ‘omics’) are being developed. The term passport, first coined in 2000, is now defined in the ABP Guidelines as the longitudinal profile and all other relevant information including training, competitions and information derived from investigations. In the 2015 World Anti-Doping Code, investigations or enquiries gathered from other sources will play an even more prominent role.

INTRODUCTION
In the modern era, certain International Sport Federations banned the use of specific substances in sport. Although specific substances were banned as early as 1928,1 it took almost 40 more years before analytical testing came to the fore. The initial prohibited lists and tests in the 1960s and 1970s focused on stimulants and narcotics but they expanded considerably over time. Doping Control Programmes became synonymous with urine tests and adverse analytical findings. Although the system became more complex with the introduction of out-of-competition testing, whereabouts provisions and blood testing, analytical testing has been only partially successful. This has been demonstrated by a number of athletes who loudly proclaimed their innocence based on passing their tests only to later confess to doping. Innovative strategies were called for to protect clean athletes.

INVESTIGATIONS
In the current World Anti-Doping Code, there are already eight means to an Anti-Doping Rule Violation (ADRV) and it is not simply the presence of a prohibited substance in a biological matrix, that is, a positive analytical test that can lead to sanctions. Article 2.2 states that the use of a prohibited substance may be established by any reliable means including witness statements, documentary evidence or evaluations of longitudinal profiling. Other sections of Article 2 refer to tampering, possession and trafficking as well as administering or attempting to administer prohibited substances. It is clear that the athletes’ entourage is the target of some of these sections.

After 1.5 years of widespread stakeholder consultation, a revised World Anti-Doping Code and International Standards were adopted at the 4th World Conference on Doping in Sport in November 2013 and will come into effect in January 2015. The importance of investigations has been strengthened and the International Standard on Testing (IST) has been renamed the International Standard on Testing and Investigations (ISTI) to reflect that change. As examples of new elements, there are requirements for antidoping organisations to automatically investigate Athlete Support Personnel in the case of any ADRV involving a minor or when those personnel have provided support to more than one athlete found to have committed an ADRV. There are further sections that address the intimidation of potential witnesses as well as a new section on prohibited association with those athlete personnel who have been sanctioned and serving a period of ineligibility. Athletes were particularly adamant that athlete support personnel, including doctors and coaches, should suffer more significant consequences as result of encouraging or aiding doping behaviour.

ATHLETE BIOLOGICAL PASSPORT
This article will principally focus on the Athlete Biological Passport (ABP) programme which is a recent paradigm that infers the use of prohibited substance (or method) by the detection of selected discriminant biomarkers which may persist long after the original substance has been metabolised or excreted. For example, the haematological module...
detects blood manipulation by the use of erythropoietic stimulating agents or via blood transfusions. It combines longitudinal analysis of biomarkers and information gathering as well as providing direction for more targeted testing for traditional analytical testing.

Serial analysis of biomarkers was already in practice by a number of federations with some programmes predating the formation of the World Anti-Doping Agency (WADA) and the implementation of the World Anti-Doping Code. However after the 2006 Torino Winter Olympic Games, at the request of a number of International Federations (IFs), WADA formed an ad hoc Haematological Working Group to look at the issue of blood doping and to develop a harmonised longitudinal profiling programme that was both scientifically and legally robust. This resulted in the creation of the ABP Guidelines and Related Technical Documents which were first published in 2009. An Anti-Doping Organisation will only be deemed to be following the WADA ABP Programme if it adheres to the mandatory elements of the related technical documents.

In 2011, WADA re-established a Haematological Expert Group to further refine and develop this module. The goal is to evaluate analytical elements and possible confounding factors with a rigorous scientific approach. For example, it is clear that fluctuations in plasma volume will have an influence on a number of the measured haematological variables (biomarkers). During exercise, plasma volume will contract before it settles back to normal levels in about 2 hours postexercise. Therefore the Technical Document on Blood Sample Collection Requirements for the ABP mandates that blood collection does not occur within 2 hours of training or competition to maintain the validity of the sample.

As of the beginning of 2014, 41 Anti-Doping Organisations run haematological ABP programmes; these are in different phases of implementation. This has resulted in more effective targeting for testing (eg, EPO tests) which contributed to the doubling of positive analytical findings for EPO in the first years of the programme. From the implementation of the ABP to the end of 2013, more than 40 cases resulted in direct sanctions (ADRVs) without the benefit of an adverse analytical finding. These have been reported by both National Anti-Doping Organisations and IFs.

Deterrent effects are hard to accurately measure without knowing the prevalence of doping in different sport populations. However there have been interesting changes in blood variables as was demonstrated in a retrospective study from 2000 to 2011. The percentage of reticulocytes outside the normal range changed significantly over the years. In 2000–2001, ~10% of cyclists had high reticulocyte percentages (Retic %) >2%, then that number dropped and close to the same percentage came in with very low Retic % as EPO testing became more widespread. Thus, athletes either stopped using EPO earlier in relation to the competition (and testing) or switched back to blood transfusions. Then after 2008, there was a return to normal population values as the Union Cycliste Internationale (UCI) began running the pilot ABP and subsequently the full ABP programme. This return to normal Retic % in cyclists could be a sign of decreased blood manipulation, although one cannot exclude highly sophisticated doping including the use of other substances. Further suggestions that the ABP may be having a deterrent effect come from performance evaluations (and from anecdotal stories and interviews of athletes). The normalisation of haematological data and significant reduction of extreme variations could also be perceived as a health benefit for the sport population.

It is interesting to note that biomarkers of doping can be a useful tool to help estimate the prevalence of doping by comparing haematological results obtained on a population of athletes of interest with reference data obtained in clinical trials involving clean and doped volunteer athletes. This was nicely demonstrated by Sottas et al in a study on elite track and field athletes.

STERoidal MODULE OF THE ABP

The steroidal module took effect on 1 January 2014; it uses the same principles and processes as the haematological module and can be used for targeting or can directly result in an ADRV. A further feature of the current steroidal module is an enhanced individualised approach to testosterone:estrogen (T:E) ratios for IRMS confirmation. Since the 1980s, a T:E ratio of initially >6:1 and then >4:1 was considered suspicious of doping. IRMS confirmation was then recommended on the sample in order to confirm the presence of an exogenous steroid. It is known that there are certain genetic polymorphisms, such as the deletion of the UGTB217 gene, that result in very low T:E ratios far below the typical 1:1. Applying a longitudinal approach with personalised upper and lower limits would take into account those with low but fluctuating T:E ratios who may have otherwise avoided this confirmation test and also decrease excessive IRMS testing in those with naturally T:E high ratios. Therefore the steroidal module will result in a more effective and efficient use of IRMS.

FUTURE MODULES AND INTEGRATION

There are new modules in the process of development to complement the haematological and steroidal modules of the ABP. Research has been directed to develop an endocrine module to look at substances that control various hormone axes, such as growth hormone. Longitudinal profiles of high level athletes are being collected to establish population-based comparisons; individual endocrine profiles for various hormones are being tested to see whether they have the potential to reveal doping. Furthermore, WADA has directed and supported research into ‘omics’ strategies from genomic to proteomic evaluations. Some ‘omics variables could be integrated in the ABP following due validation and assessment of confounding factors. Eventually the ABP may have quite a different look and these modules which are presently operating and being developed separately will become evaluated together as part of the athletes’ passport.

It is known that the use of anabolic steroids may enhance erythropoiesis, therefore it could be interesting for some athletes who are at high risk of steroid doping to have a haematological profile as well. Competition, performance results and other information such as that obtained from investigations will all be layered on top of the longitudinal profiles. It should be noted that the definition of a ‘passport’ in the Guidelines is the longitudinal profile and all other information.

DATABASE AND SHARING OF INFORMATION

Athletes may be tested by different testing authorities which may be National Anti-Doping Organisations, IFs or Major Events Organisers. Data should be entered into a secure central database system to ensure that there are no gaps in the longitudinal profiles which would interfere with the interpretation of the individual data. The goal is to have one passport for one athlete with all the data points included. All WADA accredited and approved laboratories enter the results into a central database called Anti-Doping Administration and Management...
System (ADAMS) where each athlete gets assigned an anonymous BP ID number. The Adaptive Model, a Bayesian type of statistical analysis that uses prior information, is automatically applied to these longitudinal profiles and notifications are sent to the appropriate agencies when the profile is considered atypical. However, currently not all stakeholders are using ADAMS which means that some results entered by laboratories are orphaned and not associated with the appropriate BP identity number. This diminishes the global efficacy of the ABP and prevents WADA from fulfilling its duty as a monitoring agency. WADA encourages Anti-Doping Organisations to share information and testing to increase the efficiency of the ABP, avoid duplication and to decrease costs.

Athletes’ rights must be fully respected and protected through this process which is why WADA consults ethicists, data-protection and other legal experts to ensure that basic principles such as privacy and proportionality remain entrenched.12

CONCLUSION

WADA continues to develop and improve the ABP with input from experts and stakeholders. The principles and practice of an ABP should be a model of a modern, integrated antidoping programme. This combines traditional and new analytical approaches along with non-analytical methods such as information from intelligence.

The world of sport and antidoping continues to evolve with increasing challenges. The access and supply of prohibited substances has increased dramatically in the past decades and is now readily and rapidly available via the Internet. There are newer substances including peptides and designer drugs that are harder to detect. The potential for significant financial gains in sport has encouraged the involvement of sophisticated doping entourages and networks of suppliers.

Therefore it is critical to implement and advance the new modules of the ABP in order to detect and deter doping. Ultimately, we must endeavour to create an environment that allows clean athletes to flourish and reach their full potential.

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