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Review

Detection of the misuse of steroids in doping control☆

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ABSTRACT

The list of prohibited substances of the World Anti-Doping Agency (WADA) classifies the administration of several steroids in sports as doping. Their analysis is generally performed using urine specimen as matrix. Lots of the steroids are extensively metabolised in the human body. Thus, knowledge of urinary excretion is extremely important for the sensitive detection of steroid misuse in doping control. The methods routinely used in steroid screening mainly focus on substances, that are excreted unconjugated or as glucuronides. Common procedures include deconjugation using a β-glucuronidase enzyme. Following extraction and concentration the analytes are submitted to LC-MS(/MS) analysis and/or GC-MS(/MS) analyses. Besides the classical steroids, more and more products appear on the market for "dietary supplements" containing steroids that have never been marketed as approved drugs, mostly without proper labelling of the contents. To cover the whole range of potential products comprehensive screening tools have to be utilised in addition to the classical methods.

Endogenous steroids, e.g. testosterone, represent a special group of compounds. As classical chemical methodology is incapable of discriminating synthetic hormones from the biosynthesised congeners, the method of steroid profiling is used for screening purpose. Additionally, based on isotope signatures a discrimination of synthetic and natural hormones can be achieved.

Contents

1. Introduction

The basis of human sports doping control is set by the World Anti-Doping Agency (WADA) within the World Anti-Doping Code [1]. It defines doping as mainly the presence of prohibited substances in a specimen; and the use or attempted use of a prohibited substance/method.

The list of prohibited substances covers all classes that are recognised as doping in sports and is updated each year. The list currently in action [2] comprises steroids in the following sections:

S1. Anabolic agents
   1. Anabolic androgenic steroids (AAS) and
   2. Other anabolic agents
S4. Hormone antagonists and modulators

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S5. Diuretics and other masking agents
S9. Glucocorticosteroids

The number of adverse analytical findings for these classes as reported by the accredited laboratories [3] are illustrated in Fig. 1. This data also comprises findings, especially for testosterone, corresponding to multiple measurements performed on the same athlete, e.g. from longitudinal studies.

For doping control purpose samples are collected from the athlete and partitioned into two aliquots (A- and B-sample), which are separately sealed. They are sent to the doping control laboratory only referring to a code number without indicating the athletes name.

The first screening analysis on the A-sample, which covers a wide variety of steroids, is followed by the analysis of a second aliquot of the same specimen in case of a suspicious result in screening (confirmation) [4]. Only after confirmation of the screening result the responsible Anti-Doping Organisation and the WADA are informed about the adverse analytical finding. Before sanctioning, the B-sample analysis can be requested and carried out in the presence of the athlete, his/her external representatives and/or experts [1].

The analysis for steroids in doping control is generally performed using urine specimen as matrix. The methods routinely used in steroid screening mainly focus on those metabolites, that are excreted unconjugated or as glucuronides into the urine. For sample preparation aliquots are hydrolysed enzymatically using β-glucuronidase. Extraction of the deconjugated steroids from the matrix and concentration of the analytes is performed by liquid–liquid extraction or solid phase extraction followed by mass spectrometric detection either by liquid chromatography tandem mass spectrometry (LC-MS/MS) or gas chromatography (tandem) mass spectrometry (GC-MS(/MS)). As proposed by Donike [5] most of the laboratories use N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA) as reagent for derivatisation prior to GC separation. The formation of per-TMS derivatives utilising trimethyliodosilane as catalyst has proven to drastically improve the sensitivity for most of the steroids in GC-MS-based assays [6,7]. Several compounds, most of them deuterated, composing the internal standard allow to control the critical steps of sample preparation and to determine the amounts of steroids excreted [8].

As doping control laboratories are confronted with an increasing number of substances to screen on, a comprehensive screening for steroids covering different classes of prohibited substances is desired. A procedure [9] covering all steroids in one screening method after deconjugation of the glucuronides combines LC-MS/MS and GC-MS analysis within one single sample preparation. The final residues are separated into two aliquots and analysed separately. The sample preparation is depicted in Fig. 2. Criteria for

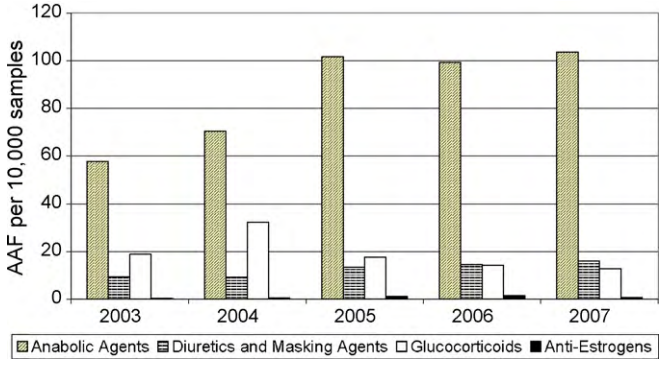


Fig. 1. Number of adverse analytical findings in doping control (per 10,000 samples) reported by WADA accredited laboratories (source WADA [3]).

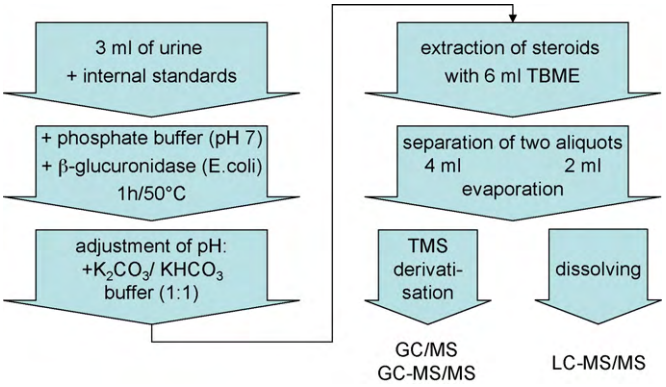


Fig. 2. Example for a comprehensive screening analysis for steroids in doping control [9].

substance identification as proposed by WADA [10] include the relative abundances of at least three diagnostic ions or ion transitions and the retention time compared to reference urines or reference substances, which have to match.

2. Endogenous steroids

Endogenous steroids are steroids, that naturally occur in individuals. The WADA list of prohibited substances [2] only specially refers to endogenous AAS as a subclass of S1. Anabolic Agents. It explicitly lists androst-5-ene-3β,17β-diol, androst-4-ene-3,17-dione, dehydroepiandrosterone (DHEA), dihydrotestosterone, testosterone and several metabolites and isomers thereof. Boldenone, nortestosterone and their prohormones respectively, could be classified as either endogenous or exogenous AAS. They may be synthesised physiologically in very small concentrations. Most likely these steroids are side products of the steroid metabolism. Transformations by intestinal bacteria are also discussed [2,11–19].

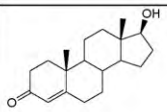
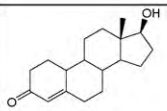
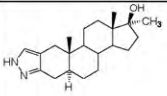
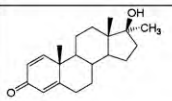
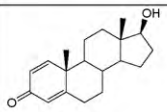
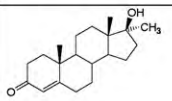
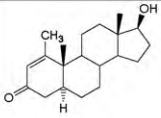
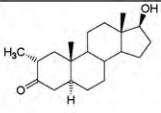
Endogenous AAS are extensively metabolised in the human body and only small amounts of the parent substances are excreted in the urine. The most important metabolic phase-I reactions include oxidation or reduction in position C-3 and C-17. Furthermore Δ4 steroids in general are substrates for reduction mainly towards 5α direction, which is reported as rate limiting step in inactivation [20]. Minor metabolic pathways include hydroxylation at various positions by different cytochrome P450 enzymes (including CYP3A4 and CYP2C9, two of the predominant liver P450s) [20,21]. The metabolic conversion of androgens, like testosterone or androstenedione, to estrogens is catalysed by Cyp19, also called aromatase. The primary metabolites resulting from this reaction, estradiol and estrone, are no target in human sports doping control.

The administration of endogenous AAS is prohibited in sports with testosterone, biologically the most important anabolic androgenic hormone, likely being the molecule with the highest potential of abuse (Fig. 3). Since 1996 so-called prohormones have been available as dietary supplements on the US sports nutrition market and are therefore easily accessible. As intermediates of steroid metabolism DHEA, androst-4-ene-3,17-dione, androst-4-ene-3,17-diol and androst-5-ene-3,17-diol are all converted to testosterone, resulting in increased testosterone levels. 19-Norandrost-4-ene-3,17-dione, 19-norandrost-4-ene-3,17-diol and 19-norandrost-5-ene-3,17-diol are metabolised to 19-nortestosterone, and androst-1-ene-3,17-dione, androst-1-ene-3,17-diol, and androsta-1,4-diene-3,17-dione are also recognized as prohormones [22–25]. Due to their conversion to active anabolic androgenic steroids their application in sports is also prohibited. Since the late 1990s it has been proven that also non-

hormonal nutritional supplements may result in positive tests in doping control due to their unlabelled prohormone content. Most likely this occurs by cross-contamination during the production process. These findings do indicate an insufficient surveillance and quality control of dietary supplements. The production evidently does not follow Good Manufacturing Practices [26–29].

As all the above mentioned steroids and their metabolites also occur naturally in the human body specific indicators for the detection of the exogenous administration of these steroids are required [30]. Following administration elevated levels of metabolites, which are part of the urinary steroidome, are proven [31–38]. Thus, for screening purposes a set of urinary concentrations of several endogenous steroids or metabolites is usually determined by the gas chromatographic-mass spectrometric (GC-MS) method used for the detection of steroid abuse (Fig. 2). This method of steroid profiling was first introduced into routine doping control by Donike et al. (testosterone/epitestosterone (T/EpiT) ratio) [31]. Some ratios of these steroids have been proven to be very stable [39–44]. The most important steroid profile parameters in doping control are the ratios of T/EpiT, androsterone/etiocholanolone, androsterone/T, and 5α/5β-androstane-3α,17β-diol. Longitudinal and retrospective evaluation of steroid profiles offer a suitable basis for individual reference ranges, which allow powerful discrimination of natural versus altered steroid profiles. However, also a comparison with population-based reference ranges is recognised as indicative of the administration of endogenous steroids. Samples showing a T/EpiT value equal or greater than 4, a concentration of T or EpiT (equivalent to the glucuronide and adjusted for a specific gravity value of 1.020) greater than 200 ng/ml, a concentration of androsterone or etiocholanolone (equivalent to the glucuronide and adjusted for a specific gravity value of 1.020) greater than 10,000 ng/ml, or a concentration of DHEA (equivalent to the glucuronide and adjusted for a specific gravity value of 1.020) greater than 100 ng/ml are recommended to be analysed by isotope ratio mass spectrometry (IRMS) for confirmation of the exogenous origin. Also other parameters can justify IRMS analysis [30].

Based on the distinct stable carbon isotope signatures ($^{13}C/^{12}C$) a discrimination of synthetic steroids and natural steroidal hor-

Name		Class of substance	No of AAF per 10,000 samples
Testosterone		S1.1.b.	71.8*
Nandrolone		S1.1.a.	9.1
Stanozolol		S1.1.a.	7.7
Metandienone		S1.1.a.	4.4
Boldenone		S1.1.a.	1.8
Methyltestosterone		S1.1.a.	1.2
Metenolone		S1.1.a.	1.0
Drostanolone		S1.1.a.	1.0

* Findings also sum up data corresponding to multiple measurements performed on the same athlete, e.g. from longitudinal studies

Fig. 3. Anabolic androgenic steroids most often detected in doping control, chemical structures, classification and number of adverse analytical findings 2004–2007.

mones can be achieved. The signature also propagates into urinary metabolites of the steroid hormones. In order to compensate for baseline variations and uncertainties of the calibration the $^{13}C/^{12}C$ ratios of AAS and corresponding metabolites are not evaluated directly but are compared to endogenous reference compounds (ERCs), which are steroids biosynthesised from androgen independent pathways (e.g. 5β-pregnane-3α,20α-diol, 5β-pregnane-3α,17α,20α-triol, 11β-hydroxyandrosterone, 11-oxoetiocholanolone, or 5α-androst-16-ene-3α-ol) [45–54]. The determination of the hydrogen isotope ratio $^{2}H/^{1}H$ was recently reported to supplement the carbon isotope measurements [55,56].

As for GC-MS detection of steroid abuse in general, the sample preparation for IRMS analysis also mainly focuses on the glucuronidated steroid metabolites [57,58]. Only few methods also apply IRMS to steroid sulfoconjugates [59,60]. However, due to the conversion of all organic compounds to CO_2 (or H_2 respectively) prior to mass spectrometric detection a sophisticated sample preparation is necessary. Thus, HPLC purification is utilised following hydrolysis [50,61] and the obtained fractions are analysed separately.

As silylating agents such as MSTFA conflict the combustion of analytes the residues are typically analysed either as free form or acetates [45–47,54,55,58].

3. Exogenous steroids

3.1. Classical synthetic anabolic androgenic steroids

A wide variety of exogenous AAS is explicitly mentioned on the list of prohibited substances [2]. The chemical structures of the most frequently detected AAS in recent doping control are shown in Fig. 3.

Metabolism of exogenous AAS in general follows analogous principles (3 and 17 reduction and oxidation, 5α-hydrogenation of Δ4 steroids and hydroxylations) as described for the endogenous AAS. However, additional double bonds in ring A or B or additional substituents in position C-4 or C-6 push the reduction towards 5β orientation. 5β-Metabolites are reported to be inactive in general [20,62]. As an example the complex metabolite pattern of metandienone is displayed in Fig. 4 [63–66]. Exemptions for AAS, which show a relatively high metabolic resistance with respect to phase-I reactions, are 3-oxo-4,9-diene, 3-oxo-4,9,11-triene and 3-oxo-1,4,6-triene steroids.

As already described for the endogenous AAS the analyses are carried out by GC-MS(/MS) and LC-MS(/MS) mostly after cleavage of the glucuronides. Some LC-MS/MS methods also use intact glucuronides or sulfate conjugates as analytes [67–70]. Special focus is given on the main and the long-term metabolites. The laboratories are obliged to test for the parent substance or metabolites with a minimum sensitivity of 10 ng/mL for anabolic agents in general and with 2 ng/mL for the metabolites of metandienone (17β-methyl-5β-androst-1-ene-3α,17α-diol), methyltestosterone (17α-methyl-5β-androstane-3α,17β-diol) and stanozolol (3′-hydroxystanozolol) [71].

In case of the detection of boldenone or its main metabolite, 17β-hydroxy-5β-androst-1-ene-3-one, in very low concentration the application of any reliable analytical method (e.g. IRMS) is recommended to determine the exogenous origin of the substance [2,72].

Also norandrosterone can be detected in urine not only due to the administration of the prohibited substances nortestosterone or its prohormones but also due to pregnancy or the administration of the non-prohibited oral contraceptive norethisterone or in women. Both sources can be checked for by the occurrence of other specific analytes (gonadotropin hCG < 5 mIU/mL for exclusion of pregnancy or tetrahydro metabolite of norethisterone). In untreated males the urinary norandrosterone concentration is generally very low [13–15,73–76]. As a result of demethylation norandrosterone is reported to be generated from C19 steroids during sample storage only in very low concentrations (<10 ng/mL of urine) [77]. Considering the above mentioned, a threshold concentration of 2 ng/mL has to be exceeded to cause an adverse analytical finding [78]. IRMS confirmation of the exogenous source has been reported to be suitable for norandrosterone concentrations in the lower ng-range to complement the analytical data [18].

As supplementary approach to traditional mass spectrometric techniques a yeast androgen receptor reporter gene system can be used to detect substances with affinity to the androgen receptor. This assay is capable of detecting a broad variety of androgens

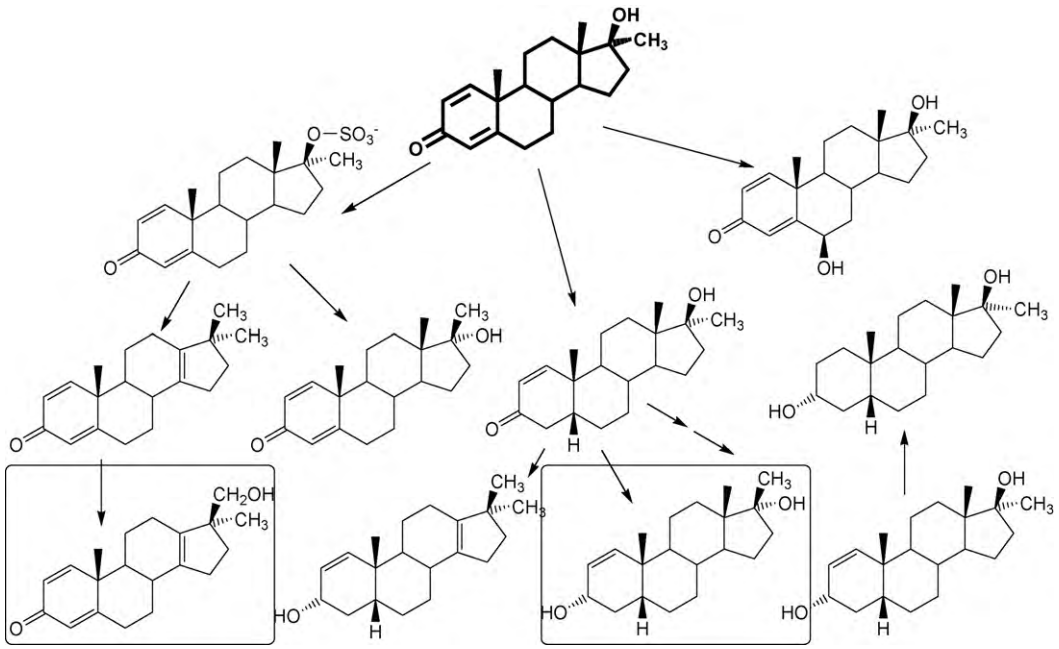


Fig. 4. Main metabolites of metandienone (bold structure) detected in human urine (current long-term metabolites in boxes) [63–66].

without knowledge about their structure. In combination with analytical methods with discriminating and identifying power, it has to be considered as useful tool to screen for unexpected anabolics [79,80].

3.2. Designer steroids

The term "designer steroid" applies for steroids, which are synthesised (or marketed, if they already existed) to evade existing laws (legal and sports), by modifying the molecular structures to produce similar effects to controlled drugs. The first designer steroid under this definition with respect to doping regulations was the medicament Oral-Turinabol containing the steroid dehydrochloromethyltestosterone. It was already synthesised in the 1960s and used up to the late 1980s by GDR athletes to circumvent doping control. From the late 1990s on, the US "nutritional supplement" company BALCO marketed the designer steroids norbolethone, tetrahydrogestrinone (THG, "The Clear"), and desoxymethyltestosterone (Madol, DMT) to athletes as "undetectable" steroids [81–85].

Since the classification of prohormones as schedule III controlled substances by the anabolic steroids control act [86] in 2005, more and more products appear on the market for dietary supplements containing steroids that were never marketed as approved drugs mostly without proper labelling of the contents [87–103]. The chemical structures of some examples are depicted in Fig. 5. Syntheses and few data on pharmacological effects are available dated back mainly to the 1950s or 1960s [104]. Only little knowledge exists about effects and side effects of these steroids in humans. Also little information is available on their metabolism. They are only produced for the "supplement market" and are advertised as anabolic steroids and/or aromatase inhibitors. The legal status of these supplements is not clear in several countries. To cover the whole range of these designer steroids comprehensive screening tools are required. Applying mass spectrometric techniques like GC-MS or LC-MS/MS offers the possibility of unknown steroid detection [105] by monitoring common fragment ions or losses indicating the principle structure and functional groups. Especially employing the precursor ion scanning option of triple-quadrupole mass analysers provides a useful tool for the detection of unknown steroids when focusing on product ions derived from common steroid structures and nuclei [106,107]. Also the above mentioned yeast assay may be useful in screening for unknown designer steroids. Structure confirmation and metabolic studies have to be performed afterwards.

3.3. Steroidal aromatase inhibitors

As indicated by their name aromatase inhibitors work by restraining the aromatase enzyme complex, which converts androgens into estrogens. As breast tissue is stimulated by estrogens, decreasing their production is a therapeutically used way of suppressing recurrence of the breast tumor tissue but also in the treatment of ovarian cancer in post-menopausal women. Aromatase inhibitors can be subgrouped into two classes: Non-steroidal inhibitors (e.g. anastrozole, letrozole), which inhibit the enzyme by reversible competition and the steroidal inhibitors (e.g. exemestane, formestane, and testolactone), which irreversibly block the aromatase by a permanent bond with the enzyme complex (also called suicidal aromatase inhibitors) [108]. In sports aromatase inhibitors and other anti-estrogenic drugs are used to minimise the side effects of anabolic steroid misuse. The elevated estrogen levels as a result of anabolic steroid aromatisation can cause unwanted water retention, fat gain and gynocomastia (the growth of breast tissue in men). Underground literature advises users to administer aromatase inhibitors to extent steroid use cycles while estrogen receptor blockers should be used to milder acute side effects. Aromatase inhibitors may also be misused as significant increases of dihydrotestosterone, free and total testosterone in serum were reported during the administration of aromatase inhibitors [109,110]. However, these findings were observed in hypogonadal men and may or may not be relevant to athletes with normal gonadal function.

According to the regulations of the World Anti-Doping Agency (WADA), steroidal aromatase inhibitors (as well as other aromatase inhibitors and anti-estrogens) are prohibited substances for use in sports [2].

As already mentioned within "designer steroids", several "new" steroids appeared on the dietary supplement market, that are advertised to result in aromatase inhibition (e.g. androst-4-

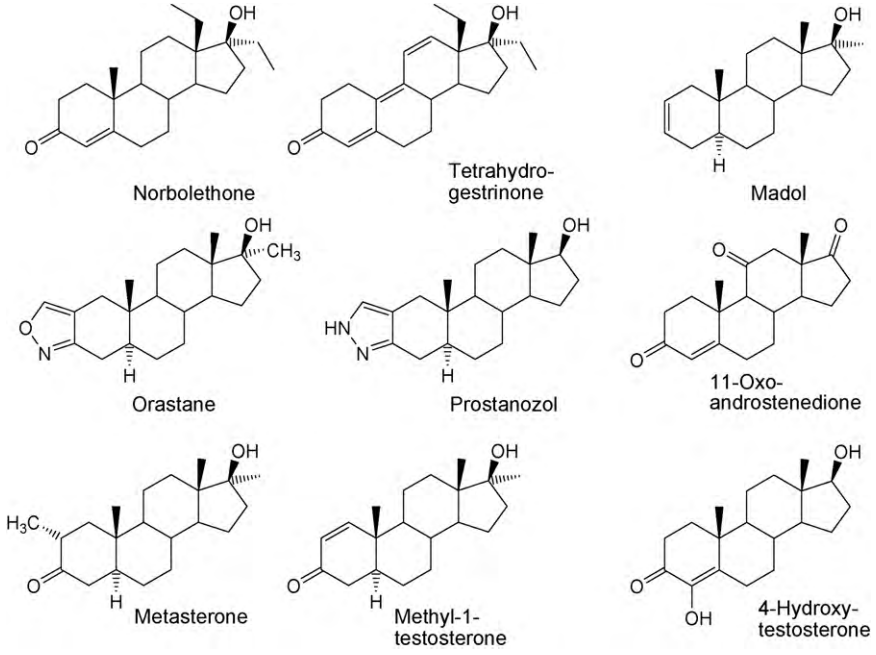


Fig. 5. Chemical structures of some examples of designer steroids with anabolic androgenic properties.

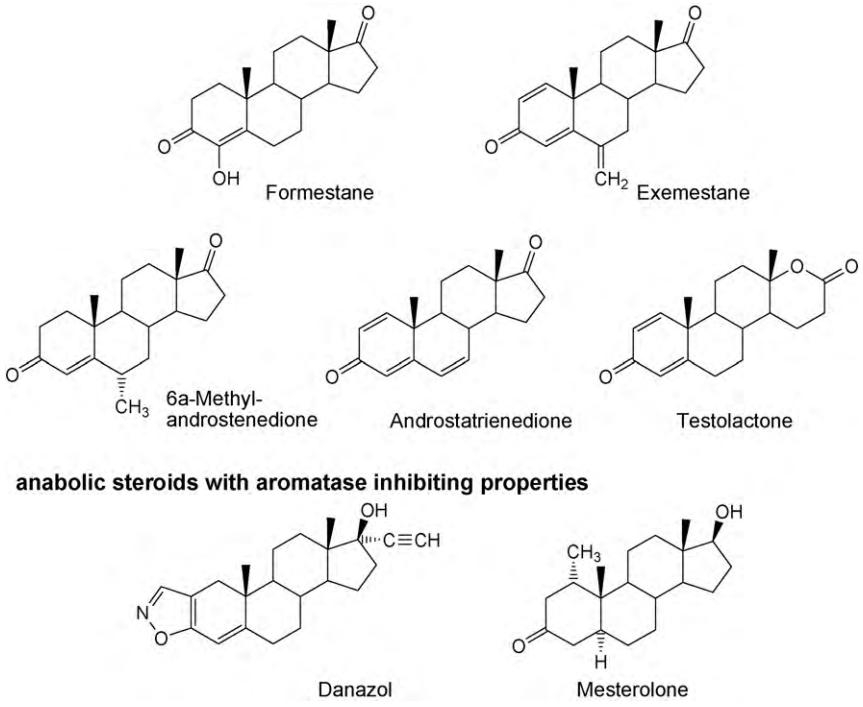


Fig. 6. Chemical structures of steroidal aromatase inhibitors and anabolic steroids with aromatase inhibiting properties.

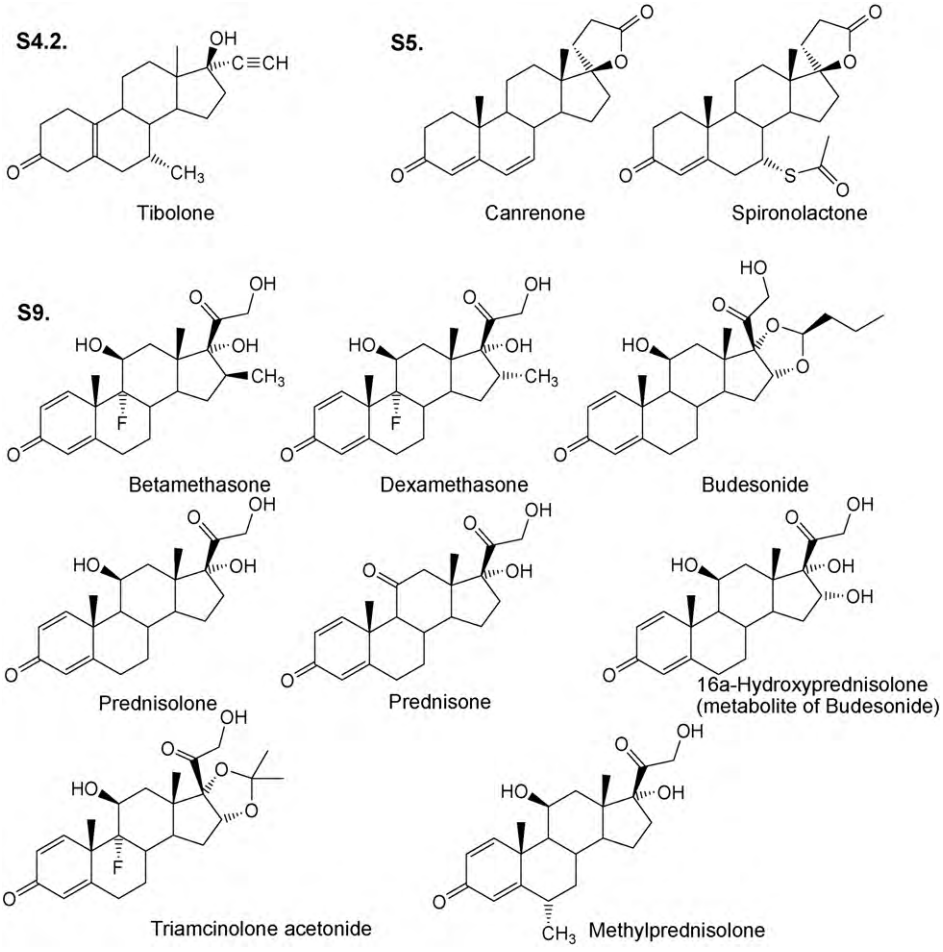


Fig. 7. Chemical structures and classification of steroids other than AAS and aromatase inhibitors detected in 2007 doping control (S1.2. other anabolic agents, S5. Diuretics and other masking agents, S9. Glucocorticosteroids) [3].

ene-3,6,17-trione in 6-OXO™, androsta-1,4,6-triene-3,17-dione in Novedex Xtreme™, and 6α-methylandrost-4-ene-3,17-dione in Formadrol™ and Methyl-1-Pro™ [89,94,96,98,100,111]).

The chemical structures of steroidal aromatase inhibitors are closely related to those of anabolic androgenic steroids and based on androstane as backbone (Fig. 6). Thus, they or their metabolites respectively can easily be incorporated into the screening procedures for anabolic androgenic steroids.

Also the anabolic steroid danazol results in a reduced transcription of the aromatase gene [112] and the anabolic steroid mesterolone is discussed in underground literature as competitive aromatase inhibitor. The chemical structures of both anabolic steroids are also displayed in Fig. 6.

3.4. Glucocorticosteroids

Glucocorticosteroids are frequently abused by athletes in sports (Fig. 1 [3]) to improve the performance due to their effects related to energy metabolism, euphoria and pain suppression. They are very potent drugs in the treatment of inflammatory processes and chronic obstructive airway diseases. Moreover, corticosteroids can ease pain in general. In adrenal insufficiency they are therapeutically used as replacements [113,114]. Glucocorticosteroids are considered as prohibited substances at in-competition testing (class S9.). Their use is prohibited, when administration is performed by oral, intravenous, intramuscular, or rectal routes. The administration by intraarticular, periarticular, peritendinous, epidural, intradermal and inhalation routes to treat medical conditions that need the administration of glucocorticoids currently requires a therapeutic use exemption (TUE) or declaration of use, while certain topical preparations do not require a TUE or declaration [2]. Most of the synthetic glucocorticosteroids are excreted as unmetabolised parent compound (chemical structures of some examples in Fig. 7) with additional 6-hydroxylated metabolites also detectable. Apart from that budesonide is excreted to a considerable extent as its main metabolite 16α-hydroxyprednisolone [115].

Conjugation of synthetic glucocorticosteroids is hampered due to the additional double bond in the A-ring and/or fluorine at C-9 [116]. Thus, detection is possible after simple extraction (either liquid–liquid at alkaline pH or SPE) from the urine. However, within combined screening procedures (e.g. [9,117]) also enzymatic hydrolysis of glucuronides (with no effect on corticosteroids) is performed. Most of the methods currently used for corticosteroid analysis utilise LC-ESI-MS/MS [117–121] as sensitive GC-MS requires derivatisation (e.g. enol-TMS or methoximes), which is time consuming, results in formation of different isomers and/or derivatives with limited stability and/or does not fit the other routinely used procedures [122–124].

3.5. Other steroidal doping agents

Tibolone (structure formula in Fig. 7) is explicitly listed as prohibited substance since January 2006 under the category 'other anabolic agents' [2]. Therapeutically it is used for the treatment of menopausal disorders (hormone replacement therapy) such as in the approved drug Liviella®. Anabolic–androgenic effects are reported besides its estrogenic activity [125–127]. Detection in doping control can be achieved by including its 3α-hydroxy metabolite into the GC-MS screening procedure [91].

Canrenone and its prodrug spironolactone (Fig. 7) are competitive aldosterone receptor antagonists acting as potassium-sparing diuretics. Besides this, they also display anti-androgenic effects and spironolactone is therefore also used in treating hair loss and acne. Diuretics are mainly misused by athletes for adjustment of weight categories or by body builders for disposal of subcutaneous water. Additionally diuretics may be administered to dilute urine samples to lower the concentration of other prohibited compounds. Subsequently the concentration of metabolites might drop below the established threshold (e.g. for norandrosterone) or below its limit of detection. In recent human sports doping control canrenone was detected in 8–15 samples per year (15 (2007), 8 (2006), 14 (2005), 9 (2004), 14 (2003)). It can be detected in routine doping control within the LC-MS/MS screening procedure displayed in Fig. 2 using positive ESI for ionisation or together with other diuretics by LC-ESI(+)-MS or LC-plasmaspray-MS after liquid-liquid extraction at pH 5.2 or by GC-MS after extractive alkylation [9,128–132].

4. Conclusion

The detection of the misuse of steroids in sports is routinely achieved by mass spectrometric techniques. Depending on the class of steroids, which influences the molecular structure and thereby also to some extent the analytical properties, preceding separation by gas or liquid chromatography is favoured. As lots of steroids are extensively metabolised, doping control analysis predominantly concentrates on the detection of specific metabolites tracing the prohibited administration. The administration of endogenous steroids can be uncovered by determination of the carbon isotope ratios. In some cases also hydrogen isotope ratios may also give appropriate information. Traditional methods for the detection are recently complemented by supplemental assays to detect also the misuse of unknown substances.

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