PROJECT REVIEW

"Confirmation of formestane abuse in sports: a metabolic approach"

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Formestane is an anti-estrogenic drug used on the treatment of breast cancer. In humans, estrogens are strong pituitary inhibitors of gonadotrophins releasing factors. The inhibition of the estrogens synthesis produces an increase of luteinizing hormone (LH) and then a net increase of testosterone production is expected. In addition the combined administration with testosterone will reduce the side effects linked to aromatization like gynecomastia. For these reasons, anti-estrogenic substances were included in 2004 in the World Anti Doping Agency (WADA) List of Prohibited substances.

The analytical methodologies developed so far are based GC/MS or LC/MS, targeting formestane itself. Traces of formestane can be produced endogenously and detected in urine samples in low concentrations (0.5-20 ng/mL) and thus, since 2011, it is mandatory according to WADA rules to perform a confirmation based on isotope ratio mass spectrometry (IRMS) in order to assess the synthetic origin of formestane before releasing an adverse analytical finding.

The IRMS developed methods require two consecutive liquid chromatographic purifications (HPLC) before obtaining extracts of adequate purity, and not all laboratories are currently prepared to perform such IRMS analyses. The metabolism of formestane analysis has been extensively described in a single male volunteer. It appears that among the high number of metabolites described 4a-hydroxy-epiandrosterone has a longer detection window. A metabolic approach based on the detection of specific metabolites of formestane may avoid the use of IRMS for the confirmation of formestane intake, thus reducing the cost and complexity of the analyses. Simultaneously in the case IRMS should still needed, the development of a method for the detection of long term metabolites, excreted for a longer time compared to formestane and in larger amounts in the elimination phase, will certainly improve the detection capacity of formestane.