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The use of cytochrome P450 inhibitors in sport. A new generation of doping masking agents?

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Abstract

The activity of the CYP450 enzymes responsible for the phase I metabolism of most of the compounds included in the World Anti-Doping Agency (WADA) list of prohibited substances and methods could be strongly modified by the combined administration of other drugs such as, for example, the antidepressant, the antifungal and the H2 receptor antagonist agents. These compounds act as inhibitors of the CYP450 isoforms and it has been demonstrated that their co-administration with a drug that is also a CYP450 substrate may lead to a substantial alteration of the latter drug bioavailability, metabolism and excretion kinetics. In sports some classes of non-banned drugs, and primarily among them antidepressants, antifungals and the H2 receptor antagonists are extensively used, according to the information available on the doping control forms. Athletes may intentionally combine the CYP450 inhibitors with doping agents to modify in urine the time window of detection of the selected marker(s) of drug abuse, especially in those cases where the parent drugs are extensively metabolized.

This research is designed to investigate whether the co-administration of CYP450 inhibitors with doping agents could be considered as a doping masking strategy. For this purpose the *in vitro* metabolic profile of representative banned compounds (toremifene, stanozolol, methandienone, ciclesonide and deflazacort) was assessed individually and in the presence of different concentrations of the selected CYP450 inhibitors (the antifungal agents fluoconazole, ketoconazole, itraconazole and miconazole; the H2 receptor antagonist agents cimetidine and ranitidine and the antidepressant agents fluoxetine, paroxetine and nefazodone).

We present here the preliminary results of this study, demonstrating that the metabolic profiles of the classes of substances (SERMs, steroids and glucocorticoids) specifically considered in this study were extensively altered in presence of ketoconazole, itraconazole, miconazole, and nefazodone; whereas moderate variations were registered in presence of paroxetine and not significant modifications were measured in presence of ranitidine, cimetidine, fluoconazole and fluoxetine.