PROJECT REVIEW

"Azole antifungals. Confounding factors or modulators"

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Azole compounds were introduced into the therapy of fungal infections of humans in the early 1970s. The primary target of azole compounds is the CYP51, the enzyme involved in the synthesis of ergosterol from lanosterol in the fungal cell membranes. However, azoles have a potential to interact also with other cytochrome P-450-dependent enzymes, leading to toxicologically relevant changes in the liver and endocrine system. Indeed, depending on their effects on specific enzymes inhibited they can cause (i) a reduced formation of either androgens or estrogens, and/or (ii) alterations in the elimination rate of xenobiotics. CYP19 (aromatase) is one of the cytochrome P450 enzyme inhibited by azoles. Several azole fungicides disrupt normal aromatase function leading to a decrease in estrogens formation, and for this reason these agents are not prescribed in pregnancy and are instead used in the management of advanced estrogen-responsive breast tumors in postmenopausal women.

Reduction of estrogen levels by CYP19 inhibition is the working principle of anti-aromatase agents. These agents together with other anti-oestrogenic compounds, are included in the section S4 "Hormone and Metabolic Modulators" of the WADA prohibited List. Azole antifungals are instead included in the WADA TDEAAS as confounding factors. In a previous WADA-funded project, focused on the evaluation of the alterations provoked by the administration of azole antifungals on the basal levels of the parameters that are part of the steroid profile, we have reported that both miconazole and fluconazole is capable of altering the levels of the endogenous steroids in a different manner. In this project we aim to extend the study by increasing the number of measurements, including more individual, different ethnicities, route of administration, doses, range of age and by evaluating whether similar effects can be caused also by other azole antifungals.