

PROJECT REVIEW

"An in vitro study on the biotransformation pathways of vaptans. Selection of the most appropriate markers of misuse"

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Vaptans are a relatively new class of compounds with diuretic suitable for publication on WADA's website effects. They increase water excretion by inhibiting its reabsorption in the renal collecting ducts. For these reasons, vaptans have been included by the World Anti-Doping Agency in the section S5 "Diuretics and Masking agents" of the list of substances and methods that are prohibited in sport. Previous investigators have reported that this class of compounds is extensively cleared by hepatic metabolism via oxidative enzymes. Consequently, the most efficacy strategy to detect them in urine samples could not be achieved by simply targeting the drug itself: the selection of one or more diagnostic metabolites is necessary. Very few data are reported in literature on the metabolic profile of these compounds in humans; at the same time, the influence of physiological and environmental factors on their excretion profile is also almost completely unexplored yet.

This project aims to define the phase I and phase II metabolic reactions and to characterize the enzymatic isoforms involved in the biotransformation pathways of vaptans. Alterations of the metabolic profile of vaptans provoked by physiological (i.e. sex, genetic polymorphism) and environmental (drug-drug interactions) factors, will be evaluated to obtain information on the impact of these factors on the biotransformation pathways detected. Finally, the possibility of obtaining sufficient amounts of vaptans metabolites by enzyme-assisted synthesis will also be explored. Human liver microsomes will be the source of the isoenzymes involved in the phase I metabolism of vaptans; the metabolites once formed will be isolated by HPLC, characterized by MS and used as reference materials to set up and validate efficacy analytical procedures to detect vaptans in urine