IN VITRO AND IN VIVO HUMAN METABOLISM OF ALBACONAZOLE

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Albaconazole (ALBA, UR-9825) is a new triazole antifungal agent that is under clinical development at J.Uriach & Cia. ALBA has shown good in vitro and in vivo antifungal activity in pre-clinical studies and an excellent tolerability in humans.
In vitro studies were carried out to identify the P450 isoenzymes involved in the metabolism of ALBA. [^{14}C]-ALBA was incubated for 4 h in pooled human liver microsomes, at concentrations ranging 1-20 µM, and yielded a single metabolite fraction in a concentration-dependent manner. The formation of this metabolite (that was later identified as hydroxy-ALBA (ALBA-OH)) was most efficiently catalysed by CYP3A4/5. The values for K_m and V_{max} were 3.1µM and 125pmol/h/mg protein, respectively. Calculated intrinsic clearance (C_{lint}) and hepatic extraction coefficient (E_h) were 0.65 ml/min/Kg and 0.13%, respectively. These results suggest low first pass effect after oral intake.

In vivo metabolism was investigated following a single oral dose of 80 mg of [14C]-ALBA in healthy volunteers (n=6). Radioactivity was excreted predominantly in feces and in urine, with means of 55.8±11.2% and 29.9±10.9% of the administered dose, respectively, after 336 hours post dose (total recovery 85.6±12.4%). In feces ALBA-OH, and its corresponding sulfate and glucuronoconjugate were found. In urine, only the conjugates were present. A small percentage (5%) of unchanged ALBA was found in feces. In plasma, the major component was ALBA, whereas ALBA-OH and its conjugates were present into a much lesser extent. Pharmacokinetic analysis of plasma ALBA concentrations showed a rapid absorption, good tissue distribution and a bi-exponential decay with a half-life of 55.3±8.9 h (mean±ES).

In summary, in vitro and in vivo studies show that albaconazole undergoes extensive and slow metabolism into a single hydroxy derivative, which in turn is transformed into two conjugate derivatives. Spectroscopic studies aimed at the determination of the position of the hydroxy group in the structure of ALBA-OH are in progress. Further studies will determine the exact contribution of these phase I and phase II metabolites to the overall antifungal activity.