
SAFETY AND PRELIMINARY PHARMACOKINETICS OF AN ORAL SOLUTION CONTAINING ALBA- CONAZOLE AFTER SINGLE AND MULTIPLE DOSE ADMINISTRATION TO HEALTHY VOLUNTEERS

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Albaconazole (ALBA, UR-9825) is a triazole antifungal agent that has showed good in vitro and in vivo activity. The aim of this study was to define safety, tolerability and plasma pharmacokinetics (PKs) of an oral solution containing ALBA after single and multiple dose administration to healthy volunteers. Two randomized, double-blind, placebo-controlled studies were performed. In the single dose (SD) study subjects received 80, 160, 240 or 320 mg. In the multiple dose (MD) study, subjects received 80 or 160 mg/q24h during 14 days. Each group of dose had 8 subjects (6 active, 2 placebo). Blood and urine samples were collected for up to 11 days (SD) or 28 days (MD) for PK analysis. Safety was assessed by physical examination and clinical laboratory testing.

A total of 48 subjects (32 SD; 16 MD) were analyzed. ALBA was well tolerated. The reported adverse events (AE) were mild or moderate and resolved prior to discharge. Headache was the most frequent AE (12 %) and it was reported by both active and placebo subjects. No clinically relevant changes were observed in biochemical, hematological, vital signs and ECG parameters. PK analysis of the SD and MD administrations showed high levels of exposure. In SD, C_{max} increased proportionally with the dose. Thus, mean C_{max} values of 0.94, 1.84, 3.24 and 3.60 µg/ml were obtained at the doses of 80, 160, 240 and 320 mg, respectively. AUC_{0-∞} values increased greater than proportionally at these doses, with values 15.1, 35.5, 60.8 and 95.3 µg.h/ml, respectively. Albaconazole was rapidly absorbed, with a mean T_{max} of 1h. Elimination half-life increased with dose (range 55 to 93h). Inter-subject variability following SD was low, with CVs ranging from 15% to 34% for C_{max} and AUC values. In MD, higher levels of exposure and half-life values were obtained after 14 days of administration. Preliminary results indicate that plasma accumulation occurs after MD treatment at high doses.

Conclusion: the single and multiple administrations of ALBA resulted in high levels of exposure that were safe and very well tolerated by all subjects. This study warrants that a wide range of dose regimes is compatible with the treatment of fungal infections with ALBA.