
LACK OF QTc EFFECTS OF ALBACONAZOLE , A NEW TRIAZOLE ANTIFUNGAL

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Albaconazole (ALBA, UR-9825) is a new, broad-spectrum triazole antifungal agent that has shown good in vitro and in vivo activity as well as an excellent tolerability in humans. Pre-clinical and clinical studies have been carried out to assess the potential of ALBA in inducing cardiac arrhythmias.

The hemodynamic effects of ALBA were investigated in anesthetized Beagle dogs. No effects on arterial pressure, heart rate, intraventricular and end-diastolic pressures, cardiac output, peripheral blood flow and ECG intervals (including QTc) were observed at doses up to 10 mg/kg iv. ALBA (60 mg/kg po) did not modify either the heart rate or QTc interval in conscious guinea pigs, whereas ketoconazole (KETO) at the same dose produced significant reductions in heart rate and increases in the QTc interval ($p < 0.01$). ALBA did not produce significant changes in action potential parameters in dog Purkinje fibers, whereas KETO increased APD90 and itraconazole reduced APD50. ALBA (10 μ M) did not block HERG potassium channel in HEK-293 transfected cells. At the same concentration ravuconazole and KETO blocked currents by 57 and 71%, respectively.

Although observations from pre-clinical data yielded no evidence of cardiac effects, the possibility that ALBA might have an action on the human heart was rigorously explored. Data from over 126 volunteers involved in four clinical phase I studies were evaluated according to the CPMP/986/96 recommendations. A total of 2872 ECGs were recorded in these studies which involved doses ranging from 5 mg up to 400 mg in single and repeated doses. Four volunteers (3.2%) reported increases in QTcB -greater than 60 msec- from baseline values. These were in the following groups: 5 mg (day 1), 20 mg (day 16), 40 mg (day 1) and placebo (day 16 and 18). No increases over 60 msec were observed in QTcF. All QT, QTcB and QTcF values were lower than 500 msec. No plasma concentration and individual QTcB values relationship was found.

In summary, the QT interval monitoring during pre-clinical and clinical studies with the new antifungal agent ALBA showed no significant effect on cardiac repolarization.