Microbiology

Mechanism of Action

Miconazole inhibits 14-α-demethylase, a microsomal cytochrome P-450-dependent enzyme system critical to sterol synthesis. Accumulation of sterols with a 14-α-methyl group in their structure also causes membrane defects manifested as a modest but significant reduction in growth rate. Interference with sterol biosynthesis increases permeability of the cell membrane.

The accumulation of ergosterol precursors and toxic peroxides results in cytolysis. Candida albicans cells have been observed to exhibit progressive cytoplasmic deterioration and permanent shape changes resulting in complete cell necrosis depending on the dose and duration of exposure to miconazole nitrate.

Low concentrations of miconazole nitrate (< 5 µg/ml) increases peroxide as the consequence of increased NADH-dependent oxidase activity. Simultaneously, the activity of peroxidase is suppressed and that of catalase is enhanced. The intracellular buildup of hydrogen peroxide in toxic concentrations may contribute to the observed degeneration of subcellular structures that precedes cell death.

Activity

Of 1328 isolates of Candida albicans, miconazole nitrate inhibited 67% at concentrations of 1 µg/ml or lower and 99.9 at 10 µg/ml or lower.

Resistance

Miconazole is widely used in prescription and non-prescription products, including extensive use for vaginal yeast infections; in addition to medical use, azole molecules are widely used in agriculture. Despite this widespread use, the only known circumstances in which resistance to azole antifungal agents has developed conspicuously, unequivocally and measurably is among HIV-infected individuals treated with fluconazole for oral Candida infections.

Among all current systemic antifungal drugs, flucytosine is the agent for which resistance resembles most closely the situation in bacteria. Because resistance to flucytosine is well known and has been studied thoroughly, it can be detected easily by determining the minimal inhibitory concentration (MIC) or by disc-susceptibility testing. Resistance to miconazole nitrate has been evaluated as a potential cause in the etiology of recurrent vulvovaginal candidiasis.
In a study of 50 patients followed, 177 isolates of *Candida albicans* collected over periods of 3 months to 7 years demonstrated no increase in minimal inhibitory concentrations (MICs). Moreover, as a result of prolonged therapy and the MICs from the majority of longitudinal isolates collected from individual women did not shift with any drug over time. (Lynch, 1996)

For these reasons, we believe the evidence supports the conclusion that *Candida albicans* would not become miconazole-nitrate resistant from the use of this antifungal for the indication of treatment of diaper dermatitis in infants.