Investigation of the *in vitro* efficacy of caspofungin, micafungin and nikkomycin Z using micro- and macrodilution methods against the major *Candida* species

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Summary

During the tests we studied the *in vitro* activity of two echinocandins (micafungin and caspofungin) against the clinically relevant *Candida* species in RPMI-1640 and in 50% human serum supplemented RPMI-1640 medium with help of micro- and macrodilution methods. The effects of nikkomycin Z and human serum were investigated in case of using caspofungin against those isolates which showed or not paradoxical growth.

Reduced micafungin and caspofungin efficacy were observed in presence of 50% human serum in terms of results against the clinically relevant *Candida* species. In the case of micafungin the MIC values closed or raised above the clinical breakpoints in presence of serum. First time-kill studies were applied to estimate the therapeutic efficacy of micafungin in 50% human serum. In base of our studies fungi which can be inhibited by high concentration of micafungin may required higher daily dosage therapy such as *C. parapsilosis*, *C. orthopsilosis* or *C. krusei.*

During our studies of caspofungin we convinced first paradoxical growth is eliminated by nikkomycin Z and 50% human serum against several *Candida* species using time-kill curves. However the paradoxical growth seems to be only an *in vitro* phenomenon, our results of nikkomycin Z on the one hand may help a clearer understanding the echinocandin induced

stress adaptation pathways. On the other hand nikkomycin Z is currently in clinical trial for its antifungal activity, the combination of NIK with other drugs may success in the treatment of mycoses. The combination of caspofungin with nikkomycin Z showed synergistic effect against several *Candida* species in our investigation.

Our results gained by using human serum may further improve the chances of these patients to recover from their disease since in case of the two echinocandins investigated, antifungal effects were found to be decreased in the presence of human serum. This inevitably implies that higher echinocandin doses would probably result in improved therapeutic effects; however, this strategy requires more investment. Our results should have to confirm by animal attempts.

Kulcsszavak: Echinocandinok, humán szérum alapú érzékenységi eljárások, paradox növekedés, nikkomycin Z és caspofungin kombináció

Keywords: Echinocandins, human serum based susceptibility testing, paradoxical growth, combination of nikkomycin Z and caspofungin