

## In Vitro Activities of Three New Triazoles (Voriconazole, Posaconazole And Ravuconazole) Compared with Fluconazole and Itraconazole against *Candida glabrata* Species

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**Background:** There has been an increase in the number of serious infections caused by non-*Candida albicans* (CA) species, especially *Candida glabrata* (CG). The MICs of CG to older azoles such as fluconazole (F) and itraconazole (I) are usually higher than CA. Recent *in vitro* studies have demonstrated increased activity of the newer triazoles against some resistant non-CA strains. However, cross-resistance between older and newer azoles has been reported. From *in vitro* studies, the E-test is a reliable test and often more convenient than the reference broth microdilution (MBT) method for determining susceptibility of *Candida* species. However, discrepancy between the NCCLS M27-A and E-test method for V susceptibility against CG has been observed, with higher MICs on E-test. We compared the *in vitro* activity of F, I, V, posaconazole (P) and ravuconazole (R) against clinical isolates of CG and compared the E-test to the NCCLS M27-A2 for determination of V susceptibility.

**Material and Methods:** A MBT was performed, according to the NCCLS M27-A2, on 99 clinical isolates (37 from blood and 62 from other sterile body fluids) of CG vs. F, I, V, R and P. In addition, V was also tested by E-test (AB Biodisk, Solna, Sweden). Frozen MIC panels (TREK Diagnostics, Westlake, Ohio) were read at 48 h and E-tests were read at 24 h and 48 h. The MICs of the azoles were defined as the lowest concentration of each agent in which a prominent decrease in turbidity as compared to control was observed. Susceptibility was defined as MIC  $\leq$  1  $\mu$ g/ml for V, P and R,  $\leq$  8  $\mu$ g/ml for F and  $\leq$  0.125  $\mu$ g/ml for I.

Results : Drugs	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC range ( $\mu$ g/ml)	%Susceptible
<b>Voriconazole</b>				
E-test (24 hr)	0.12	0.5	0.032->32	91
E-test (48 hr)	0.25	2	0.032->32	89
MBT(48 hr)				
<b>Voriconazole</b>	0.25	0.5	0.008-8	92
<b>Posaconazole</b>	0.5	1	0.06-4	93
<b>Ravuconazole</b>	0.5	1	0.008-8	93
<b>Fluconazole</b>	8	32	0.25-256	71
<b>Itraconazole</b>	0.5	2	0.06->16	1

The MICs of V from 48 hr E-test and MBT were comparable with 98 % and 94% agreement (+/- 2 dilution) at 24 h and 48 h respectively. V, P and R were 100% susceptible against F-and I-susceptible (S) and susceptible dose-dependent (S-DD) CG isolates by using 48 hr MBT whereas V was 96% and 90 % susceptible against F-S and F-SDD CG isolates by using E-test. Of all F-resistant (R) isolates, 100%, 88% and 88% had higher MICs (>1  $\mu$ g/ml) with V, R, and P respectively. Decreased activity of V was noted among 4 % of F-S and 10% of F-S-DD isolates by using E-test at 48 h. This resistance pattern was not seen with the MBT results.

**Conclusion:** Voriconazole, posaconazole and ravuconazole were more active *in vitro* than itraconazole and fluconazole against *Candida glabrata*. There was evidence of cross-resistance in almost all of fluconazole resistant isolates. Discrepancy ( $\geq$  +3 dilution) between the NCCLS M27-A and E-test method for V susceptibility against CG was < 5%.