

EFFICACY OF CASPOFUNGIN COMBINED WITH AMPHOTERICIN B OR FLUCONAZOLE AGAINST AZOLE-RESISTANT CANDIDA ALBICANS

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Background: Unacceptably high mortality of patients with disseminated candidiasis even with therapy necessitates the search for new, more effective treatment approaches, such as combination therapy. This study evaluates the activity of Caspofungin (CFG) combined with either Amphotericin B (AMB) or Fluconazole (FLC) against azole-resistant *Candida albicans*.

Methods: In vitro (checkerboard) and in vivo (murine disseminated candidiasis model) systems were used to evaluate the effects of combination. For in vivo assessment, BALB/c mice (7 per group) were challenged (5×10^5 yeast, I. V.), and treated (2 weeks) with CFG (0.002 mg/kg) alone or combined with either AMB (0.016 mg/kg), or FLC (0.64 mg/kg). Survival and tissue fungal burden (expressed as CFU) were determined. CFUs were compared using Mann-Whitney U-test ($P < 0.05$ was considered significant).

Results: Combining CFG with AMB or FLC, in vitro, resulted in synergistic and additive effects (Fractional inhibitory concentration index were 0.075 and 0.75), respectively. Mice treated with CFG+AMB survived longer compared to the groups treated with CFG+FLC, AMB alone or FLC alone as well as untreated mice. Kidney CFUs were reduced following treatment with CFG+AMB compared to untreated control, FLC-, and CFG-treated groups ($P=0.05$, 0.002, 0.05, respectively). Reduction in brain CFUs were observed using CFG+AMB compared to untreated controls, FLC, AMB & CFG+FLC treated mice ($P=0.005$, 0.002, 0.05, 0.02, respectively).

Conclusion: Our data shows that combining CFG with either AMB or FLC resulted in synergistic and additive interactions in vitro, respectively. Moreover, CFG+AMB prolonged mice survival and reduced tissue burden. The clinical implication of these findings is yet to be determined.