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ePoster Viewing
Antifungal drug susceptibility and resistance

Optimising antifungal combination therapy of voriconazole+amphotericin B against Aspergillus fumigatus using a pharmacokinetic-pharmacodynamic (PK-PD) model

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Objectives: Polyene-triazole combination therapy is often used for the treatment of refractory invasive aspergillosis. *In vitro* this combination demonstrated concentration dependent synergistic and antagonistic interactions raising questions on the role of therapeutic drug monitoring (TDM) for optimization of antifungal combination therapy. We therefore investigated the pharmacodynamic effects of voriconazole+amphotericin B combination against *A. fumigatus* isolates simulating human serum concentration-time profiles in a new *in vitro* PK-PD model and determined the serum concentrations that maximize the synergistic and minimize the antagonistic interactions.

Methods: The clinical isolate of *A. fumigatus* ATCC MYA-3626 with voriconazole and amphotericin B CLSI MICs of 0.5 and 1 mg/L, respectively, was used. Voriconazole and conventional amphotericin B serum concentration-time profiles were simulated in a newly developed *in vitro* PK model with a half-life of 6h for voriconazole and 2h and 12h for the alpha and beta elimination phase, respectively, of amphotericin B. Twenty-one different combination regimens including monotherapies and drug-free control were investigated simulating various voriconazole and amphotericin B fC_{max}s (7.2, 3.4, 1.7, 0.8, 0.4 mg/L and 2.4, 0.6, 0.3, 0.1, 0.05, 0.025, 0.012 mg/L, respectively). After inoculation with 10^3 CFU/mL, voriconazole and amphotericin B were added in to the model alone and in combination every 12h and 24h, respectively for 3 days and incubated at 37°C. Drug levels were determined by microbiological diffusion assays and fungal growth by measuring galactomannan production using a commercially available sandwich-ELISA (Biorad). The % of fungal growth was calculated based on the area under the galactomannan-time curve, while drug interactions were analyzed using the Bliss independence model. All experiments were carried out in duplicate.

Results: Most combination regimens exerted independent effects (4-9%). Synergy (23-34%) was observed for combinations with voriconazole fC_{max} 1.7 mg/L and amphotericin B fC_{maxs} ≤0.1 mg/L. Combination regimens with voriconazole fC_{max} 0.8 mg/L and amphotericin B fC_{maxs} 0.1 and 0.05 mg/L also exerted synergistic effects (19-31%), whereas antagonism (-32 - -29%) was found at lower amphotericin B fC_{maxs} ($p<0.05$). Extrapolating to human dosages and taking into account the protein binding of voriconazole (58%) and amphotericin B (95%), the fC_{maxs} where synergistic interactions were observed can be achieved in human plasma after standard dosing of voriconazole (4 mg/kg) and amphotericin B (1 mg/kg) (Purkins *et al* AAC 2002, Ayestarán *et al* AAC 1996).

Conclusion: The double combination of voriconazole plus amphotericin B may be synergistic against *A. fumigatus* at clinically achievable serum concentrations, particularly in patients with sub-therapeutic drug concentrations, where antagonistic interactions may also occur, enhancing the necessity for TDM of combination regimens.