Impact of dosing frequency on azole's pharmacodynamics against Aspergillus fumigatus

Antigoni Elefantzi, Maria Siopi, Nikolaos Siafas, Loukia Zerva, Joseph Meletiadis
Clinical Microbiology Laboratory, Attikon University Hospital, Athens, Greece

Correspondence: Joseph Meletiadis, 1 Rimini str, Haidar 124 62, Athens Greece, Tel: +30-210-583-1909, Email: jmeletiadis@med.uoa.gr

Isolates: Four clinical A. fumigatus isolates previously tested in an experimental model of aspergillosis (Mavridou et al. 2010 and Sf 54 and Sf 6), were selected: one with type isolate with no MIC recorded and three isolates with the same minimal inhibitory concentration (MIC) MIC = 3.125 (P < 0.05), 1.562 (P < 0.05) and 0.781 mg/L for voriconazole and 0.39 mg/L for itraconazole, respectively. All isolates were tested in triplicate.

Methods: To evaluate the impact of dosing frequency on fungal pharmacodynamics in vitro with and without a simulated serum, we performed a PK/PD model (Supporting Information) by comparing the estimated AUC against non-linear pharmacodynamic theory. The q24 PK/PD model was developed in previous studies and was used in this study to simulate different PK/PD dosing regimens and to evaluate the impact of frequency on fungal pharmacodynamics.

Invasive pulmonary aspergillosis (IPA) is a life-threatening complication affecting hematological neoplastic patients and haemopoietic stem cell transplant recipients particularly those with graft versus-host disease. Among the different Aspergillus species implicated in these infections, Aspergillus fumigatus is the most common cause of IPA. Voriconazole (VOR) and posaconazole (POS) belong to the second generation azoles and represent the first choice antifungal for treatment and prophylaxis, in immunocompromised patients, despite the efficacy of these agents against Aspergillus spp., the emergence of azole resistance in Aspergillus fumigatus (AFM) has led to intense research in optimizing antifungal treatment against these isolates. Invasive aspergillosis is a major cause of death in immunocompromised patients. According to a recent study by the National Aspergillus Surveillance Group, approximately 20% of patients with invasive aspergillosis die within 30 days of diagnosis. The emergence of azole resistance in Aspergillus fumigatus (AFM) has led to intense research in optimizing antifungal treatment against these isolates. Invasive aspergillosis is a major cause of death in immunocompromised patients.

Materials and Methods

The 5P-15D relationships for both correlative points of the fungal growth inhibition versus log_{10}MIC for VOR (Figure 2A) and POS (Figure 2B) are shown. The MIC for voriconazole for clinical and non-clinical isolates was 0.39 mg/L for the 24-hour (q24) dosing regimen. The MIC for posaconazole was 0.781 mg/L for the 24-hour (q24) dosing regimen.

AUC against non-linear pharmacodynamic theory. The q24 PK/PD model was developed in previous studies and was used in this study to simulate different PK/PD dosing regimens and to evaluate the impact of frequency on fungal pharmacodynamics.

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Aspergillus fumigatus isolates tested in simulated serum with and without a PK/PD model (Supporting Information) by comparing the estimated AUC against non-linear pharmacodynamic theory. The q24 PK/PD model was developed in previous studies and was used in this study to simulate different PK/PD dosing regimens and to evaluate the impact of frequency on fungal pharmacodynamics.