E016

2-hour Educational Workshop

Optimising antifungal therapy - bridging laboratory and clinical expertise

Where does TDM make sense?

J. Meletiadis[1]

[1]*Attikon University Hospital, Athens, Greece*

Antifungal therapy can be associated with significant toxicity and poor clinical outcome for some patients and type of fungal infections. In order to increase efficacy and reduce toxicity, therapeutic monitoring (TDM) has been recommended. Although randomized clinical trials addressing its clinical benefit are limited, TDM is indeed an appealing approach towards personalized therapy. TDM has been recommended in case of non-compliance, non-linear pharmacokinetics, poor absorption, narrow therapeutic window, drug-drug interactions, toxicity, breakthrough infections and infections by resistant isolates. These characteristics fit for mould-active azoles (voriconazole, posaconazole and itraconazole) and flucytosine for which there is also evidence of exposure-effect and/or exposure-toxicity relationships. There is no evidence to support TDM of amphotericin B and echinocandins whereas for fluconazole TDM may be indicated in limited clinical cases (e.g. critically ill patients in haemofiltration). The following target trough concentrations of itraconazole, voriconazole and posaconazole are recommended for prophylaxis/treatment: >0.5/>0.5 mg/l, >1/>1-2 mg/l and >0.7/>1-1.25 mg/l, respectively, whereas a trough concentration <4-6 mg/l is recommended in order to avoid toxicity of voriconazole. In case of flucytosine, a trough concentration of >20-40 mg/l and a peak concentration <100 mg/l is recommended in order to increase efficacy and minimize toxicity, respectively. These levels derived from specific patient's populations and type of fungal infections and may not be applied to all clinical settings. TDM may be favored in patient populations where pharmacokinetics are not well characterized (children, neonates, elderly, obese, with organ dysfunction, under haemodialysis, haemofiltration, or extracorporeal membrane oxygenation), in case of changing pharmacokinetics (physiological instability, critical illness, diarrhea, iv-to-oral switch), in presence of interacting drugs (e.g. antacids, histamine antagonists, proton pump inhibitors etc.) and in particular type of infections (CNS, multifocal, disseminated). Of a particular interest is the use of TDM for maximizing efficacy against resistant isolates like azole-resistant *Candida* and *Aspergillus* isolates. Preclinical and clinical studies indicated that a trough concentration/EUCAST MIC ratio of 1-4 is related with maximal efficacy of voriconazole and posaconazole against *A. fumigatus* isolates whereas for fluconazole an AUC/EUCAST MIC ratio of >100 should be targeted against *Candida* infections. Various methods (bioassay, HPLC or mass spectrometry) that differ in simplicity, sensitivity and specificity have been used for TDM of antifungal drugs. TDM should be performed within the first week (3-7 days) of therapy and regularly repeated to ensure that serum concentrations are stable and within the therapeutic range particularly when there is change in dosage, formulation or other clinical parameters (e.g. deteriorating condition, addition of interacting drug). Concluding, TDM of voriconazole, posaconazole, itraconazole and flucytosine could reduce toxicity and increase efficacy particularly for patients with unpredictable pharmacokinetics and difficult-to-treat infections.