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Poster Session VI
PK/PD of antifungals and miscellaneous antibacterials

A PHARMACOKINETIC RATIONALE FOR ALTERNATE DOSING STRATEGIES OF ANIDULAFUNGIN

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Background: Little is known about the pharmacokinetics (PK) of anidulafungin (ANF) given in alternate dosing strategies other than the standard once daily schedule though these may offer a more convenient way of providing prophylaxis to patients at high risk for invasive fungal diseases. We set out to explore this in a cohort of patients admitted for an allogeneic HSCT or to receive intensive chemotherapy for AML.

Methods: We defined two groups of 10 patients that were to receive 200 mg q48h (group 1) or 300 mg q72h ANF (group 2) respectively on the day of HSCT or immediately following chemotherapy. ANF was given at a higher infusion rate of 2mg/min and continued for 14 d. Blood samples were drawn daily. In addition, two PK curves were constructed after 1 and 2 weeks of treatment at 14 predefined time points. ANF was analysed by a validated UPLC-fluorescence method and a population pharmacokinetic model was developed using nonlinear mixed-effects modelling (NONMEM 7.2 ; pirana 2.8).

Results: Of 26 patients, 20 (group 1 (n=10: 3F, 7M) and group 2 (n=10: 2F, 8M) had fully evaluable PK. The mean age was 55 yr (range 21-64) and weight 77 kg (range 52-113). A two-compartment model best fitted the data. In the final model the central volume of distribution proved to be dependent on the lean body weight (linear function) and clearance on the concomitant use of cyclosporine A (CsA : dichotomous) (P?<?0.01 and P< 0.001 respectively). Dosing group, liver function, neutropenia, renal function and albumin did not influence the PK parameters. In the final model PK parameters were: CL (without CsA) : 1.49 L/h; CL (with CsA) : 1.02 L/h ; V1: 31.8 L (for median LBM of 57 kg) ; V2: 23.1 L and Q: 0.591 L/h. Boot strapping (n=1000) confirmed the validity of the model. Both ANF regimens were well tolerated. We recorded 3 SAEs judged not related to ANF. No IFI occurred during the study.

Conclusions: Alternate dosing strategies with either 200mg q48h or 300mg q72h provide a suitable alternative to daily dosing. We have now sufficient evidence to define an optimal regimen based on modelling and simulation and demonstrate its value in clinical practice.