

P0116 Population pharmacokinetics of micafungin in critically ill patients

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Background: Drug dosing in critically ill and obese patients remains a hot topic for clinicians. The objective of our study is to describe micafungin pharmacokinetics in ICU patients by developing a population pharmacokinetic model. This approach will allow us to identify whether disease severity, ICU-specific characteristics and obesity affect patients' exposure to micafungin and to assess the adequacy of the current dosing strategy in terms of PK/PD target attainment.

Materials/methods: A pharmacokinetic, multiple-dose clinical study was conducted in the ICUs of Attikon and Ippokrateion General Hospitals of Athens. 14 patients enrolled in the study representing a population with varying degrees of obesity and severity of illness. 40% of this population (6/14) were obese with BMI > 30, while the mean SOFA score was 9 with a range from 3 to 17. All patients received Micafungin in a 100 mg dose per day. 210 plasma samples were collected, following dense sampling, with multiple pharmacokinetic curves per patient. The population PK analysis was performed using non-linear mixed effects modelling in NONMEM® (version 7.3). Patient characteristics and measurements were screened as potential covariates, according to the stepwise covariate modeling approach. The final model was evaluated based on diagnostic plots, bootstrapping and visual predictive checks.

Results: Micafungin concentration – time course was best described by a two-compartment model, with first-order elimination. The PK parameters were estimated with precision, as it is indicated by the relatively low standard errors and bootstrap confidence intervals. The estimates of the parameters with the accompanying inter-individual variability measured as CV% were Clearance (CL)=1.23L/h (21%), central volume of distribution (V1)=14L (23%), peripheral volume of distribution (V2)=11.6L/h (47%), and inter-compartmental clearance (Q)=3.12L/h (30%). Inter-occasion variability was estimated for the different sampling intervals 27.1% for CL and 38.1% for V1. Aspartate aminotransferase (AST) was found to be a covariate on Clearance, following the relationship $CL = 1.23 * (AST/40)^{-0.234}$.

Conclusions: The PK model we developed characterizes well the pharmacokinetics of micafungin in the specific population and can be used for simulations for different scenarios and PK/PD targets. Micafungin presents a moderate inter-individual variability, while the observed effect of AST measurement seems to be clinically insignificant.

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