Oral

[O27-1] O27-1: Pharmacometrics (1)

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[O27-1-3] When covariates and inter-occasion variability do not necessarily improve the performances of population pharmacokinetic (popPK) models used for therapeutic drug monitoring: the case of micafungin

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Background
It has been extensively described that covariates (COV) and inter-occasion variability (IOV) can decrease respectively the inter-individual and residual variability in parametric (P) popPK modelling, whereas in non-parametric (NP) approaches, COV and IOV may affect the number/size of support points. Our objective was to develop P and NP models with and without covariates and IOV (P-0, NP-0, P-IOV, NP-IOV, P-COV, NP-COV, P-COV-IOV and NP-COV-IOV) and to compare estimated AUCs in an independent validation dataset.

Methods
Data collected from 58 patients on 3 occasions (days 0, 4 and 14) were split into two datasets: development (43 patients, 86 PK profiles, 370 concentrations) and validation (15 patients, 36 profiles, 154 concentrations) datasets. popPK models were developed with Monolix (P) and Pmetrics (NP). The investigated COV were plasma albumin, bilirubin and creatinine, SOFA score, burn status, age, and weight, and their relevance was based on decrease of AIC. Correlation coefficient r was calculated between observed and individual predicted concentrations. AUCs were estimated from the predicted concentrations and biases versus NP-0 or P-0 were calculated. AUCs were compared using a Friedman test for paired samples.

Results
A two-compartment model including bilirubin on Ke and V (P) and burn status on Ke (P and NP) was retained. P and NP model parameters were highly different. COV inclusion was relevant for both the P and NP models, whereas IOV was relevant only for the P model. Final models described adequately the observed concentrations (r: NP-COV and NP-0=0.96;NP-IOV and NP-IOV-COV=0.95;P-0=0.97; and P-COV, P-IOV, P-COV-IOV=0.96). In the validation dataset, AUC estimated with or without IOV and COV were very similar for P (median[min-max] relative bias P-IOV/P-0=-0.65[-4.46;4.15]%;P-COV/P-0=-0.14[-6.59;4.87]%;P-IOV-COV/P-0=-0.37[-7.89;2.82]%) while the difference was larger for NP: NP-IOV/NP-0=-0.27[-46.9;48.8]%;NP-COV/NP-0=-1.42[-38.2;53.2]%;NP-IOV-COV/NP-0=1.02[-46.9;61.2]%. There was no significant difference between the 8 sets of AUC estimates (p=0.951), whereas Bland-Altman between AIC-based best models (P-COV-IOV and NP-COV) showed that 2 out of the 36 AUCs were out of the 95%CI interval.

Conclusions
When models tightly fit the data, COV and IOV may not add values when a sufficient number of concentrations is available. The high differences between P and NP may be explained by P shrinkage.