A467 - Poor reliability of creatinine clearance estimates in predicting fluconazole exposure in liver transplant patients

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Introduction:
Invasive candidiasis (IC) is a frequent complication in liver transplant (LT) recipients, especially during the first 1-3 months after LT. Fluconazole is a triazole antifungal used for prophylaxis and treatment of IC. Due to its renal elimination, dose adjustments are usually based on estimated creatinine clearance (eCrCL). However, the reliability of eCrCL in predicting fluconazole clearance has never been investigated in this population. The aim of this study was to conduct a population pharmacokinetic (popPK) analysis in a cohort of LT patients who underwent therapeutic drug monitoring (TDM) in order to find out which covariates may influence fluconazole pharmacokinetics (PKs).

Methods:
This retrospective study included LT patients who were admitted to the intensive care unit of our University Hospital between December 2007 and May 2016, and who were treated with intravenous fluconazole in the first months after LT. TDM of fluconazole was performed with the intent of attaining the efficacy pharmacodynamic target (AUC24h/MIC > 55.2).
The tested covariates were: age, gender, CKD-EPI eCrCL, time from LT, serum albumin and transaminases, SAPS II score. PopPK was carried out with Pmetrics software.

Results:
Nineteen patients (mean±SD age, weight and serum creatinine of 60±8.4 years, 75±16.8 kg, 1.0±0.62 mg/dL, respectively) with a total of 89 fluconazole trough plasma concentrations were included in the popPK analysis. Mean±SD fluconazole distribution volume (Vd) and clearance (CL) were 27.02±10.78 L and 0.55±0.19 L/h. Age and time from LT were the only clinical covariates significantly correlated with fluconazole Vd and CL, respectively. Conversely, CKD-EPI eClCr was unable to predict fluconazole CL.

Conclusion:
CKD-EPI eClCr is unreliable in predicting fluconazole exposure in LT recipients. Consistently, in this population adaptation of fluconazole dose should be based on measured CrCL, and TDM may be helpful in optimizing drug exposure.