1568. The Pharmacodynamic–Toxicodynamic Relationship of AUC and CMAX in Vancomycin-Induced Kidney Injury

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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. Vancomycin induces exposure-related acute kidney injury [AKI]; yet the toxicodynamic (TD) driver for toxicity (area under the curve [AUC], vs. maximum concentration [CMAX] vs. trough concentrations [CMIN]) remains unclear. Recent vancomycin guidelines now recommend monitoring AUC over troughs. Here we employed our translational rat model with intensive dose fractionation and sensitive FDA qualified urinary biomarkers to better understand TD relationship.

Methods. Male Sprague-Dawley rats received intravenous (IV) vancomycin via an internal jugular vein catheter. Total daily doses of 300 and 400 mg/kg/day were administered as a single, twice, thrice and four times a day injection over 24 hours. Controls received IV saline. Plasma sampling was conducted via a second dedicated jugular catheter, with up to 8 samples in 24 hours. Twenty-four-hour urine was collected during this time and assayed for kidney injury molecule 1 (KIM-1) and other urinary biomarkers using the MILLIPLEX MAP Rat Kidney Panel. Vancomycin in plasma was quantified via LC-MS/MS. PK analyses were conducted using Pmetrics for R. PK exposures during the first 24 hours (i.e., $AUC_{0-24hours}$, $CMAX_{0-24hours}$) were calculated from Bayesian posteriors. Pharmacokinetic-toxicodynamic (PK-TD) relationships were assessed with the best fit mathematic model (e.g., exposure-response curve fitting in GraphPad v.7).

Results. Sixty-four vancomycin treated and control rats contributed to PK-TD data. An exposure-response (via 4-parameter Hill) model was identified for $AUC_{0-24hours}$ vs KIM-1 ($R^2 = 0.62$, Figure 1a). Convergence was not obtained for exposure-response models for $CMAX_{0-24hours}$ and CMIN, which was also verified visually (Figure 1b and c). Despite the intensive fractionation, $AUC_{0-24hours}$ and $CMAX_{0-24hours}$ were highly correlated ($P < 0.001$, rho = 0.89) and this correlation was consistent across KIM-1 values (Figure 2).

Conclusion. Vancomycin-induced kidney injury was driven by $AUC_{0-24 hours}$ and not CMIN. Continuous infusion studies are needed to understand if changing the infusion profile can improve safety; however, these studies suggest that isometric AUCs may result in similar toxicity. When using intermittent infusion schemes, clinicians should focus on AUC to prevent AKI.

Figure 1. 4-parameter Hill fit for (a) Log_2 KIM-1 vs. Log_{10} $AUC_{0-24hrs}$ and (b) Log_2 KIM-1 vs. Log_{10} $CMAX_{0-24hrs}$ and (c) CMIN vs. KIM-1
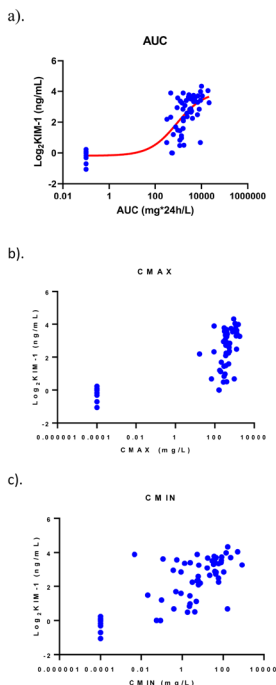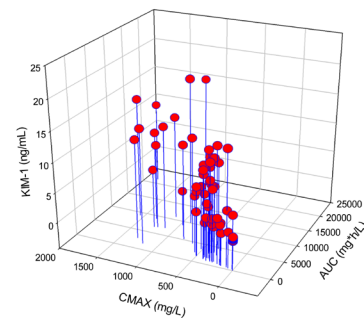
a).

b).

c).

Figure 2. 3D-Scatter Plot of KIM-1(z-axis), $AUC_{0-24Hrs}$ (x-axis) and $CMAX_{0-24Hrs}$ (y-axis) for all 64 Animals

Disclosures. All authors: No reported disclosures.

1569. A Translational Model to Assess the Impact of Polymyxin B Dose Fractionation on Kidney Injury

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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. Progression of antimicrobial resistance has revived Polymyxin B (PB) use in clinical practice. Dose-dependent acute kidney injury (AKI) limits its clinical use. It is unclear whether dose fractionation of total daily dose can lessen kidney injury. We assessed the role of PB fractionation on AKI in a translational model that employs sensitive urine biomarkers qualified by the FDA.

Methods. Male Sprague–Dawley rats received 12 mg/kg/day PB subcutaneously for 3 days or equal-volume normal saline (NS). PB was administered in 3 separate fractionated daily doses: 12 mg/kg daily (QD), 6 mg/kg twice daily (BID), and 4 mg/kg thrice daily (TID). Staggered blood sampling was done on days 1 to 4 and 24 hour urine was collected at baseline, on days 1, 2, and 3. Plasma creatinine (Cr) was quantified using LCMS/MS, and 24 hour urinary biomarkers (KIM1, OPN, CLN, calbindin, GSTα, IP-10, TIMP-1, and VEGF) were assayed with MILLIPLEX Rat Kidney Toxicity Magnetic Bead Panel. Mixed-effects models were used.

Results. A total of 32 rats contributed to the study data. Mean Cr were constant across groups over time (Figure 1, $P = 0.18$). For NS group, all biomarkers remained at baseline throughout study. Significant differences were seen for fractionation schemes for KIM1 ($P = 0.02$), CLN ($P = 0.03$), IP-10 (0.007) and TIMP-1 ($P = 0.04$). The differences for KIM1, IP-10, and TIMP-1 were driven by higher observed values in TID than those of BID as early as day 1 ($P < 0.04$). Furthermore, CLN was elevated for TID when compared with BID at baseline ($P = 0.048$). Similarly, TID group had the highest (but non-significant) elevations for IP-10 and TIMP-1 compared with QD on study days. Amongst all urine biomarkers, KIM1 in TID exhibited the most rapid rise from baseline to day 2 (Figure2, $P < 0.0001$).

Conclusion. In this translational model in which a single total daily dose was fractionated, sensitive urinary biomarkers indicated that TID dosing was worse than BID or QD dosing; dose fractionation of PB may lead to increased AKI. In addition, KIM1 rose rapidly as an early marker for AKI. Further efforts are needed to investigate the PK-TD relationship of PB in order to decrease AKI.

**Fig.1 PB Dose Fractionation:
Plasma creatinine in treatment groups**