A translational rat model to assess kidney function changes and urinary biomarkers with the addition of piperacillin-tazobactam to vancomycin

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Introduction

- Vancomycin (VAN) is a commonly used antibiotic which often causes vancomycin-induced kidney injury (VIKI). The primary mechanism of VIKI is acute tubular necrosis in the proximal renal tubules.[1]
- Recent meta-analyses have found the combination of VAN and piperacillin-tazobactam (TZP) to cause greater increases in serum creatinine (SCr) than VAN alone. However, SCr as a surrogate marker may not reflect overt kidney damage or loss of function.[2,3]
- In contrast to human data, previous animal studies have shown that more sensitive and specific markers of renal injury, such as kidney injury molecule-1 (KIM-1), are not elevated when TZP is added to VAN.[4,5]
- We employed a translational rat model to assess kidney function by glomerular filtration rate (GFR) using a transdermal continuous monitoring device in rats receiving VAN +/- TZP, TZP alone, or control (saline).[6]

Methods

- Four groups of male Sprague Dawley rats received VAN 150 mg/kg/day intravenously (n=7), TZP 1400 mg/kg/day intraperitoneal (n=6), VAN+TZP (n=11), or saline (n=6) for 4 total days (Figure 1).
- Real-time GFR was measured with a transdermal sensor at baseline (prior to drug dosing), and after each dose was given.
- For the GFR measurements, fluorescein isothiocyanate (FITC)-sinistrin was administered intravenously. Fluorescence was monitored via a transdermal sensor (MediBeacon, Mannheim, Germany) for 2 hours at baseline and 4 hours after each daily dose. GFR was then calculated from FITC-sinistrin clearance curves using a 3-compartment model with linear baseline correction.
- Urine samples were collected every 24 hours and urinary KIM-1 excretion was determined using a multiplex rat kidney toxicity bead panel (Luminex X-MAP, Austin, Texas).
- Spearman correlations between renal injury (KIM-1) and function (GFR) were analyzed per day. A mixed effects model (StataCorp, College Station, Texas) was used to compare GFRs and KIM-1 levels among the treatment groups, and by day of dosing.

Results

- A total of 30 male Sprague Dawley rats were included in the study.
- Most rats experienced a non-significant decline in GFR after the first dose was given.
- In a direct comparison of the VAN+TZP vs. VAN alone groups, rats which received VAN had a significant decline in GFR by day 4 (Figure 2: -0.36 mL/min/100 g body weight, 95% CI: -0.68 to –0.05).
- When the saline control was used as the referent group, rats which received VAN had a significant decline in GFR by day 4 (Figure 3: -0.56 mL/min/100 g body weight, 95% CI: -1.11 to -0.01).
- Rats in the VAN group did not recover the GFR decline and had progressive functional decline, whereas rats in all other groups subsequently recovered their GFR over the study course (Figure 3).
- Urinary KIM-1 analysis showed that compared to the saline control group, rats in the VAN group had significantly elevated urinary KIM-1 levels on day 4 (Figure 4: 74.5 ng, 95% CI: 14.6 to 134.5).
- Compared to the within-group baseline KIM-1 levels, only rats in the VAN group had significant KIM-1 elevations on days 1, 2, 3, and 4.
- KIM-1 was significantly correlated with GFR (higher KIM-1 expression with lower GFR) on day 3 (Spearman's Rho: -0.63, p<0.001).

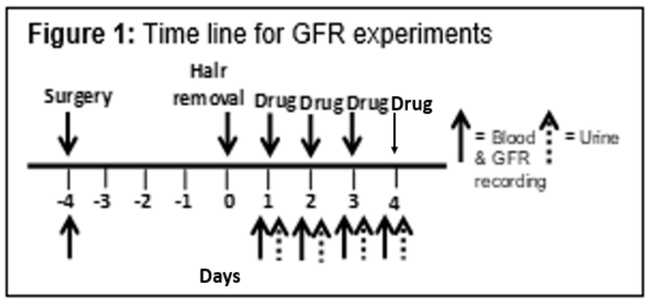

Figure 1. Timeline for experimental drug dosing, GFR measurement, and sample collection.

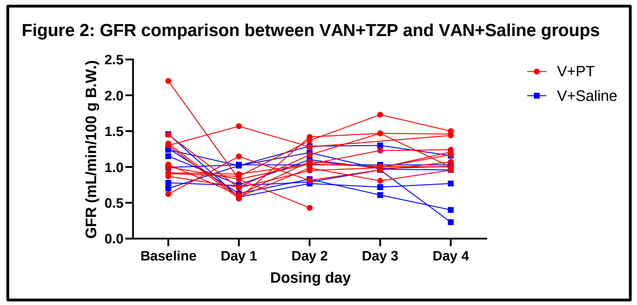

Figure 2. GFR comparison by dosing day, for VAN+TZP vs. VAN+saline groups

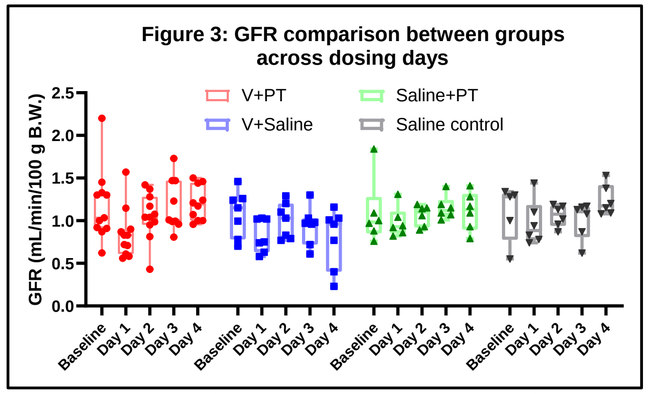

Figure 3. GFR comparison between treatment groups, across dosing days

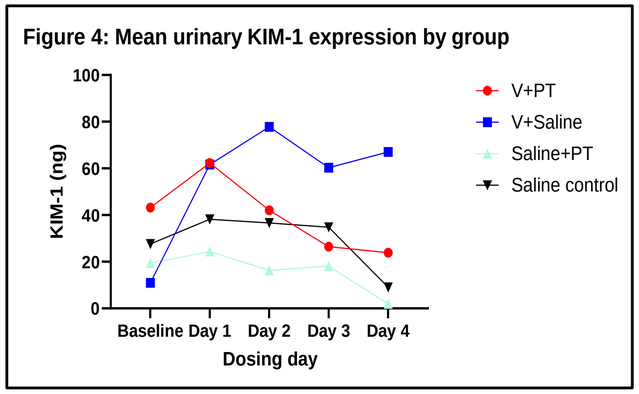

Figure 4. Mean urinary KIM-1 expression (renal injury biomarker) by treatment group.

Conclusion

- In our translational rat model assessing kidney function and injury, rats that received VAN had significant decline in GFR by day 4. This decline in kidney function was not observed in other groups (including VAN+TZP).
- The addition of TZP to VAN does not worsen kidney function (as measured by GFR), nor does it increase the expression of renal injury biomarkers (as measured by KIM-1).
- Consistent with previous animal models of nephrotoxicity, our data shows TZP does not cause additive nephrotoxicity and may be protective in the short term (days 1-4).

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