Comparison of the Nephrotoxicity of Vancomycin in Combination With Cefepime, Meropenem, or Piperacillin/Tazobactam: A Prospective, Multicenter Study

Brandon P. Mullins, PharmD1, C. Joseph Kramer, PharmD2, Billie J. Bartel, PharmD3, Jennifer S. Catlin, PharmD4, and Richard E. Gilder, RN-BC, MS2

Abstract

Background: Patients often receive broad-spectrum antibiotics for nosocomial infections commonly with activity against Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus. Previous retrospective and/or single-center studies have suggested that the combination of vancomycin and piperacillin/tazobactam might be associated with an increased risk of acute kidney injury. Objectives: To compare the incidence of nephrotoxicity in patients receiving intravenous vancomycin in combination with cefepime, meropenem, or piperacillin/tazobactam. Methods: This was a prospective, multicenter observational study of patients receiving vancomycin in combination with piperacillin/tazobactam versus cefepime or meropenem. Adult patients 18 years of age or older who were hospitalized and received 72 or more hours of intravenous vancomycin and 72 hours or more of cefepime, meropenem, or piperacillin/tazobactam were eligible. Patient and medication characteristics were examined for the 242 patients included. Results: The incidence of acute kidney injury for patients treated with vancomycin and piperacillin/tazobactam was significantly higher than for those treated with vancomycin and cefepime or meropenem, 29.8% versus 8.8%, respectively, \( P < 0.001 \). Binary logistic regression demonstrated that patients receiving vancomycin and piperacillin/tazobactam were 6.7 times more likely to develop acute kidney injury compared with the other cohort. Conclusions: The combination of vancomycin with piperacillin/tazobactam significantly increases the risk of acute kidney injury compared with other broad-spectrum antibiotic combinations. Clinicians should be vigilant when employing this regimen.

Keywords
vancomycin, nephrotoxicity, antibiotics, beta-lactams, cephalosporins

Background

Empiric antimicrobial coverage for health care–related infections typically includes multiple broad-spectrum antibiotics, specifically those with activity against Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus, as well as other likely pathogens.1,2 Choice of which agents to use depends on several factors including local susceptibility patterns as well as patient-specific characteristics (ie, recent history of antibiotic use and drug allergies). In the previous decade, antibiotic use has increased 36%, with the largest increases seen with broad-spectrum penicillins, cephalosporins, fluoroquinolones, and carbapenems.3 This trend is likely to continue and it is important to ensure that all safety concerns with these agents are fully understood.

Until recently, acute kidney injury (AKI) was not a major concern when selecting between anti-pseudomonal

1St Luke’s Hospital, Chesterfield, MO, USA
2Baylor Scott and White Research Institute, Dallas, TX, USA
3Avera McKennan Hospital and University Health Center, Sioux Falls, SD, USA
4CoxHealth Medical Centers, Springfield, Missouri, MO, USA

Corresponding Author:
Brandon P. Mullins, St Luke’s Hospital, 232 S Woods Mill Road, Chesterfield, MO 63017, USA.
Email: Brandon.Mullins@stlukes-stl.com
beta-lactams; however, recent literature has raised concerns about the potential AKI occurrence with piperacillin/tazobactam (PT) in combination with vancomycin. Vancomycin nephrotoxicity is a well-documented concern that has persisted since the drug’s introduction, but cases are generally mild and reversible. Many risk factors for vancomycin-induced nephrotoxicity exist: prolonged treatment duration, vancomycin concentrations >15 mg/L, use of concurrent nephrotoxic agents, and certain host factors (history of AKI, chronic kidney disease [CKD], and admission to the intensive care unit).

Previously, 3 retrospective studies were published examining the correlation of AKI in conjunction with PT or cefepime. In one study of patients treated for osteomyelitis, Moenster and colleagues reported the incidence of AKI for vancomycin + PT (VPT) and vancomycin + cefepime (VC) to be 31.2% and 19.5%, respectively, but this difference was not statistically significant. In another retrospective study, it was found that patients had a 34.8% incidence of AKI compared with only 12.5% of VC patient (95% confidence interval [CI] 1.89-7.39, P < 0.0001). Last, a third study published looked at cases receiving vancomycin with and without PT and reported that patients in their study who were receiving VPT were almost 2.5 times more likely to develop AKI than those patient receiving vancomycin alone (95% CI >1.11, P = 0.032).

While this study was being conducted, 3 additional publications were found examining this subject. A single-center, retrospective study examining VPT versus VC in critically ill patients conducted by Hammond and colleagues did not find a difference in the rates of AKI (VPT 32.7% vs 28.8%, P = 0.761). Likewise, a meta-analysis of 11 studies of vancomycin versus VPT and 5 studies of VPT versus vancomycin combined with another beta-lactam found similar results. Vancomycin alone had lower rates of AKI compared with VPT (odds ratio [OR] 3.980, P < 0.001) but the comparison of VPT versus vancomycin + beta-lactam had similar rates of AKI (OR 3.029, P = 0.063). Last, a small, single-center study compared VPT with VC or vancomycin + meropenem (VM), similar to our study, and found the rates of AKI for VPT to be 37.3% versus 7.7% for the VC/VM group, P = 0.005.

Based on the conflicting results of the aforementioned studies and the uncertainties that remain with certain broad-spectrum antibiotic combinations, this prospective study was designed to compare the incidence of AKI in patients receiving intravenous (IV) vancomycin in combination with cefepime, meropenem, or PT.

Methods

Study Design and Outcomes

This was a prospective, multicenter observational study examining the incidence of AKI in patients receiving IV vancomycin in combination with cefepime, meropenem, or PT. This study was conducted at 4 medical centers around the United States (see the appendix for full list of participating institutions). The study was approved by all institutional review boards of the participating institutions before collection of data. The primary objective of this study was to determine if there is a difference in the incidence of AKI in patients receiving a combination of IV vancomycin with PT versus meropenem or cefepime. For the purposes of this investigation, the definition of AKI is a minimum 1.5-fold increase in serum creatinine (SCr; baseline vs maximum within first 7 days of antimicrobial therapy) similar to previous studies. Secondary objectives were to determine if the presence of the following risk factors increased the incidence of AKI for patients receiving the above-mentioned antibiotic combinations: intensive care unit admission, concomitant use of nephrotoxic agents (see the appendix), age ≥65, certain comorbid disease states (see the appendix), or vancomycin trough concentrations ≥15 mg/L. All participating institutions used a 4-hour extended-infusion of PT rather than standard intermittent infusion of 30 minutes.

Participants

Adult patients 18 years of age or older who were hospitalized and received 72 or more hours of IV vancomycin and 72 hours or more of cefepime, meropenem, or PT were eligible for inclusion into this study (antibiotics must overlap for at least 48 hours). Patients were excluded from the study if they had a documented history of CKD (K/DOQI stage 3 or higher), baseline SCr ≥ 1.5 mg/dL, or AKI at any time during their hospital stay prior to receipt of study antibiotics (defined as creatinine clearance [CrCl] < 30 mL/min via Cockcroft-Gault or a 1.5-fold increase in SCr or greater). If at any time a random or trough vancomycin concentration was measured <10 mg/L before discontinuation of therapy the patient was excluded as this does not represent an adequate steady-state vancomycin regimen. Additionally, if a patient switched from one stratification of antibiotics to another or if they received any dose of the study antibiotics between hospital admission and enrollment into the study they were excluded. Furthermore, if a patient suffered cardiac arrest before initiation of antimicrobials they were excluded.

Data Collection

The following patient information and laboratory values were recorded from the electronic medical records of the participating institutions: age, gender, weight, height, concomitant nephrotoxic agents, comorbid disease states, Charlson Comorbidity Index, dosing regimen and duration of specified antibiotics, SCr concentrations (initial and maximum), vancomycin concentrations (trough and random), hospital unit, length of hospital stay, incidence of renal...
replacement therapies (RRT), time to resolution of AKI, primary infection site, if sepsis type of sepsis (not indicative of primary site of infection), and SCr at day of hospital discharge or last measured SCr. Vancomycin concentrations obtained before steady state (before fourth scheduled dose) or trough concentrations drawn >2 hours before the next scheduled dose were regarded as random concentrations. If a steady-state trough concentration was obtained between 2 and 1 hours prior to the next scheduled dose the value was extrapolated using population-based pharmacokinetic equations (see the appendix). Patients were followed from time of inclusion until hospital discharge.

**Statistical Analysis**

To detect a 10% difference in the incidence of AKI between VPT and VC or (VM) groups, a sample size of 540 patients (270 in each arm) was estimated to achieve a statistical power of 80% based on the estimates of a 25% risk of AKI in the VPT group and 15% AKI in both the VC and VM groups. Chi-squared or Fisher exact test were used for differences in nominal data. Comparisons between continuous data were performed using Student’s *t* test, median test, or Mann-Whitney *U* test, as appropriate. A multivariate analysis was performed to determine if certain characteristics or medications were independent risk factors for development of AKI. The Type I error (α) probability is 0.05. A *P* value of 0.05 or less was considered statistically significant for the purposes of this study. A prespecified subgroup analysis was performed of patients in the VPT arm to identify any additional risk factors for developing AKI. A preplanned interim analysis at 200 patients was conducted to surveil for an overwhelming difference or no difference between cohorts based on previous reports. This was done to ensure no further delay of potentially significant results would ensue.

**Results**

Between December 2014 and August 2016, 740 patients were screened for inclusion into the study, of which 242 patients were included. Ninety-four patients received VPT and 148 received either VM (47) or VC (101). A total of 498 patients were excluded mostly due to having baseline CKD stage 3 or higher or development of AKI before initiation of antimicrobials (Table 1). There were no differences in Charlson Comorbidity Index or any other baseline characteristics between patient groups (Table 2). During a prespecified interim analysis, there was a significant difference between the 2 groups for the primary outcome, and thus, patient enrollment was stopped before the target sample size was reached.

Most patients in the study were being treated for respiratory infections or skin and skin structure infections (Table 3).
Septic shock (%) 5.3 (5/94) 6.8 (10/148) 0.651
Severe sepsis (%) 8.5 (8/94) 8.8 (13/148) 0.941
Sepsis (%) 25.5 (24/94) 20.3 (31/148) 0.338
None (%) 60.6 (57/94) 64.1 (94/148) 0.577

Median individual dose (mg) 1250 1250 0.598

Patients receiving VPT were at a higher risk of developing AKI than those who received VC or VM (OR 6.65, 95% CI 2.79-15.84, P < 0.001). Additionally, patients receiving loop diuretics (OR 3.27, 95% CI 1.42-7.53, P = 0.005) or vasopressors (OR 5.04, 95% CI 1.66-15.35, P = 0.004) were also at increased risk of developing AKI. Last, any patient with a maximum vancomycin trough >30 mg/L was also at increased risk of AKI (OR 13.33, 95% CI 3.13-56.77, P < 0.001). Other variables analyzed were not found to be associated with the development of AKI.

A prespecified subgroup analysis of the 94 patients receiving VPT showed 3 significant risk factors for the development of AKI. Patients receiving VPT plus either a loop diuretic (42.5%, P = 0.012) or vasopressors (85.7%, P = 0.003) had a further increased risk of AKI occurrence. Additionally, VPT patients that had a maximum trough value ≥30 mg/L also had the same increased risk (100%, P = 0.024); however, this only encompassed 3 patients.

Table 5. Vancomycin Characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VPT (n = 94)</th>
<th>VC/VM (n = 148)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median individual dose (mg)</td>
<td>1250</td>
<td>1250</td>
<td>0.598</td>
</tr>
<tr>
<td>Duration of Tx (hours)</td>
<td>131.7</td>
<td>153.7</td>
<td>0.681</td>
</tr>
<tr>
<td>Minimum trough (mg/L)b</td>
<td>16.3</td>
<td>15.2</td>
<td>0.180</td>
</tr>
<tr>
<td>Maximum trough (mg/L)</td>
<td>19.6</td>
<td>18.9</td>
<td>0.619</td>
</tr>
<tr>
<td>mg/kg/dose</td>
<td>14.9</td>
<td>15.0</td>
<td>0.895</td>
</tr>
<tr>
<td>mg/kg/day</td>
<td>29.1</td>
<td>29.7</td>
<td>0.692</td>
</tr>
</tbody>
</table>

Abbreviations: VPT, vancomycin + piperacillin/tazobactam; VC, vancomycin + cefepime; VM, vancomycin + meropenem.

Table 6. Concomitant Nephrotoxic Agents.

<table>
<thead>
<tr>
<th>Medication (%)</th>
<th>VPT (n = 94)</th>
<th>VC/VM (n = 148)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>29.8</td>
<td>31.8</td>
<td>0.777</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>1.1</td>
<td>2</td>
<td>1.000</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>1.1</td>
<td>1.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0</td>
<td>0.7</td>
<td>1.000</td>
</tr>
<tr>
<td>Calcineurin inhibitor</td>
<td>0</td>
<td>3.4</td>
<td>0.160</td>
</tr>
<tr>
<td>IV contrast</td>
<td>44.8</td>
<td>37.2</td>
<td>0.282</td>
</tr>
<tr>
<td>IV immunoglobulin</td>
<td>0</td>
<td>0.7</td>
<td>1.000</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>50</td>
<td>50.7</td>
<td>1.000</td>
</tr>
<tr>
<td>NSAID</td>
<td>8.5</td>
<td>11.5</td>
<td>0.404</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>2.1</td>
<td>3.4</td>
<td>0.709</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>7.5</td>
<td>11.5</td>
<td>0.380</td>
</tr>
</tbody>
</table>

Abbreviations: VPT, vancomycin + piperacillin/tazobactam; VC, vancomycin + cefepime; VM, vancomycin + meropenem; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal antiinflammatory drug.

Discussion

This was the first prospective, multicenter study exploring differences in the development of AKI between patients receiving VPT and VC/VM. Like other studies, VPT was associated with an independent, increased risk of AKI, which was further compounded by the concomitant use of loop diuretics, vasopressors, and, potentially, vancomycin concentrations greater than 30 µg/mL. These risk factors seem to make logical sense and can be interpreted in a variety of ways given the difficulty in assessing the onset of injury and the delayed manifestation of kidney failure. It is unclear in our study whether the loop diuretics and vasopressors were the cause of kidney injury, a signal of a more complex patient population, or more likely, a combination of the two. While focusing on the associated toxicity of vancomycin concentrations, it is not clear whether elevated
vancomycin concentrations were causative of AKI or rather kidney injury that led to accumulation.

The mechanism of observed nephrotoxicity with the combination of VPT is still unclear, as is whether the combination is truly nephrotoxic. While vancomycin has clearly reported risk factors associated with the development of AKI, PT is not as simple. In point of fact, one published report evaluated rates of AKI with amikacin with or without piperacillin, and suggested a lower rate of AKI with the combination than with amikacin alone. It is unclear and needs further evaluation as to whether the combination of VPT itself is nephrotoxic or if piperacillin and/or tazobactam enhances the already nephrotoxic potential of vancomycin. The previously reported data on this topic unfortunately did not routinely evaluate the requirement of renal replacement therapy in this context. Interestingly, 2 studies did report this and found lower rates of renal replacement therapy in the VPT group than in the control group. In the present study, all patients that required renal replacement therapy (n = 3) were in the VPT cohort. Questions have also been raised regarding the accuracy of SCr in diagnosing AKI in this setting. As a competitive inhibitor of tubular secretion, piperacillin can increase the accumulation of nephrotoxic drugs into the renal tubules, as well as reduce the excretion of creatinine. This may raise questions about using SCr as a marker of AKI in this context; however, 56% of patients with AKI never returned to baseline during the observation period, and those that did return to baseline took, on average, 164 hours to return to baseline, which may argue against tubular secretion as a sole contributor.

Using a prospective, multicenter, observational design, we attempted to enhance the strength and quality of this study over previous retrospective and/or single-center cohorts. A previously reported meta-analysis attempts to remedy the limitations of the observational studies, but naturally remains inadequate by inherent limitations of these analyses within the larger model. There are also limitations within our analysis. A possible type II error exists in the separate comparison of vancomycin and meropenem. Due to the study stopping early and the smaller amount of patients in the VM arm, it is possible that VM indeed does have a higher rate of nephrotoxicity, and we feel this should be explored further before coming to a conclusion. Controlling for the impact of AKI risk and patient complexity is imperfect, although we did evaluate Charlson Comorbidity Index and concomitant nephrotoxins, as in previous publications. Additionally, our study was not able to examine the mechanism behind the cause of nephrotoxicity and is an area for future research to pursue. Last, this study does not answer the question of whether novel biomarkers, such as tissue inhibitor of metallopeptinase-2 and insulin-like growth factor binding protein-7, can assist in antibiotic management decisions through measuring renal stress and damage before AKI develops. Future studies should consider using these methods to help delineate renal damage risk and occurrence rates.

The findings of our research, in addition to other previously published studies, should allow clinicians to clearly recognize the risks of using VPT as initial empiric antimicrobial therapy. The decision of which anti-pseudemonal agent to use is largely based on local susceptibility patterns, site of infection, and individual patient factors. Clinicians should incorporate these into the decision-making process to adequately weigh risks and benefits for each patient. In this study, we did not include any patients with a history of CKD stage 3 or higher or with ongoing AKI prior to enrollment, but it might be prudent to avoid VPT combination altogether for this group of patients. More important, it is the opinion of these authors that early, broad-spectrum antibiotic use may be helpful in the management of severe infections, but commonly, indefinite combination therapy is rarely warranted. Thus, we recommend that clinicians employ appropriate culture-based and non–culture-based organism identification techniques as soon as possible to encourage antimicrobial deescalation and, thus, minimize the risk of this particularly significant adverse event.

**Conclusion**

Our data further substantiates that of earlier data to suggest an independent association between the combination of VPT and AKI. We suggest that our data, along with other published data, should be used to guide clinicians in the management of antibiotic selection. Keeping in line with core measures and best practice statements from national organizations, empiric antibiotic selection should continue to be based on local susceptibility patterns and suspected sites of infection. Additionally, the focus should be primarily on reducing overall antibiotic exposure, and secondarily, a consideration should be made to select other combinations of broad-spectrum antibiotics to avoid the toxic combination of vancomycin and piperacillin/tazobactam. Last, the authors recommend daily monitoring of SCr, appropriate antibiotic deescalation, and avoidance of identified concomitant nephrotoxins if possible.

**Appendix**

Concomitant nephrotoxic agents surveilled for the following:

- ACEIs/ARBs
- Acyclovir
- Aminoglycosides
- Amphotericin B
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Colistin
- IV contrast
- Intravenous immune globulin
- Loop diuretics
Comorbid disease states surveilled for the following:

- Diabetes
- Chronic obstructive pulmonary disease
- Heart failure (all diagnoses)
- Coronary artery disease
- Peripheral vascular disease

Pharmacokinetic equations:

- $ke = 0.00083 \times (\text{CrCl}) + 0.0044$
- Extrapolated trough = vancomycin concentration $\times e^{-ke \times t}$
  - $t$ = time difference from lab value to actual trough time

List of participating institutions

- St. Luke’s Hospital, Chesterfield, MO
- CoxHealth Medical Center, Springfield, MO
- Baylor Scott and White Health, Dallas, TX
- Avera McKennan Hospital and University Health Center, Sioux Falls, SD

Declarations of Conflicting Interests

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Supplemental Material

Supplementary material is available for this article online.

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