Comparison of acute kidney injury in patients prescribed vancomycin in combination with piperacillin–tazobactam or cefepime for diabetic foot infections

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ABSTRACT

Concomitant therapy with vancomycin (VAN) and piperacillin–tazobactam (PTZ) has been associated with acute kidney injury (AKI). Diabetic patients may be more susceptible to AKI due to various factors. In an observational, retrospective, cohort study of adults treated for diabetic foot infections (DFIs), rates of AKI were compared between groups receiving VAN+PTZ versus VAN+cefepime (CFP). Among 356 patients screened for inclusion, 210 were analyzed. Forty-nine of 140 patients (35%) in the VAN+PTZ group and 5 of 70 patients (7%) in the VAN+CFP group developed AKI according to the Acute Kidney Injury Network criteria (OR 7.00 (95% CI 2.64 to 18.53), p<0.001). After adjusting for baseline differences, VAN+PTZ was an independent predictor of AKI (OR 6.21 (95% CI 2.30 to 16.72), p<0.001). Time to AKI was 102.1 hours (IQR 47–152.7) in the VAN+PTZ group versus 78.3 hours (IQR 39.8–100.6) in the VAN+CFP group (p>0.999). Median length of stay was significantly higher in the VAN+PTZ group at 11.9 days (IQR 7.9–17.8) versus 7.8 days (IQR 4.9–12.1) in the VAN+CFP group (p<0.001). VAN+PTZ was also associated with higher total hospital charges at US$99,742.83 (IQR US$69,342.50–US$165,549.59) compared with US$74,260.25 (IQR US$48,446.88–US$107,396.99) in the VAN+CFP arm (p<0.001). In conclusion, VAN+CFP should be the preferred empiric regimen in patients with severe DFI.

INTRODUCTION

Diabetic foot infection (DFI) is a serious complication of diabetes. According to the Infectious Disease Society of America's Clinical Practice Guidelines for the Diagnosis and Treatment of Diabetic Foot Infections, broad-spectrum empiric therapy is warranted for patients with severe illness or those at risk for infections caused by multidrug-resistant organisms, including methicillin-resistant *Staphylococcus aureus* and *Pseudomonas* spp.[1]

Hospital-acquired acute kidney injury (AKI) is responsible for an estimated annual healthcare expenditure of 10 billion dollars in the USA.[2] AKI is described as an abrupt deterioration in renal function occurring over several hours or days that is often linked to broad-spectrum antimicrobials.[3 4] Diabetic patients may be more susceptible to drug-induced nephrotoxicity due to pathophysiological changes that occur in the tubular system of the diabetic kidney along with other predisposing factors.[5 6]

Although the incidence of vancomycin-induced AKI has been frequently assessed, studies evaluating the nephrotoxic potential of combination therapy with vancomycin and beta-lactams have only recently emerged. Several recent studies suggest piperacillin–tazobactam may be associated with higher rates of nephrotoxicity when used in combination with vancomycin (VAN+PTZ) compared with cefepime combination therapy (VAN+CFP).[7–13] Given the increased susceptibility to AKI, the proportions in diabetic patients may be even higher. AKI is also consistently correlated with an increase in length of stay, with reports ranging from 2 days to greater than 10 days.[2]

The recent literature examining the risk of AKI for these combinations have yet to establish distinct patient populations where avoidance of VAN+PTZ combination may be warranted. Compared with the general population, combination therapy with VAN and either PTZ or CFP is often definitive and continued for extended periods for DFIs. Previous studies excluded patients with baseline renal insufficiency as well as chronic kidney disease (CKD) stage 3 or greater, limiting the generalizability to populations at high risk of developing AKI. Furthermore, length of stay and costs associated with each regimen have not been assessed. Therefore, the purpose of this study was to determine whether a VAN+PTZ or a VAN+CFP empiric regimen for DFI would be preferred based on rates of AKI, length of stay, and total costs.

METHODS

This was an Institutional Review Board–approved (IRB201902214), observational, retrospective, cohort study conducted at

UF Health Jacksonville between February 1, 2012 and November 30, 2019.

Adult inpatients with DFI were identified via International Classification of Disease, ninth or tenth revision codes extracted from the medical record.[14] Patients who received VAN+PTZ or VAN+CFP initiated within 24 hours of each other, were treated with the combination for at least 48 hours, and had at least one vancomycin serum concentration were analyzed for inclusion. Patients were excluded if diagnosed with febrile neutropenia, received >24 hours of PTZ or CFP before switching to the other agent, pregnant, incarcerated, taking investigational medication, or documented history of CKD ≥stage IV. Standard 4-hour extended-infusion dosing regimens of PTZ (4.5 g every 8 to 12 hours) and 3-hour extended-infusion regimens of CFP (2 g every 8 to 12 hours) were used. A pharmacist-managed pharmacokinetic consultation service using trough-based monitoring for vancomycin was available for all enrolled patients.

The primary endpoint was the incidence of AKI via the Acute Kidney Injury Network (AKIN) classification in patients receiving VAN+PTZ compared with VAN+CFP for the treatment of DFIs.[15] Secondary endpoints included rates of AKI per RIFLE and vancomycin consensus guideline, length of stay, total hospital charges, and time to AKI defined as the initiation of the second antibiotic of the combination to encountering AKI.[15–17] The various AKI definitions were used to ensure that other investigators and clinicians could compare our data with any of the published literature on this topic or drug-induced AKI.

Differences between the two groups were evaluated using the nonparametric Wilcoxon rank sum test for continuous data and the χ^2 test or Fisher's exact tests for categorical data. A sample size of 70 patients per group was required to achieve a statistical power of 80% based on estimates of an 11% rate of AKI in the VAN+CFP group and 30% in the VAN+PTZ group from local and recent literature.[8 9] Treatment comparisons are presented as ORs and 95% CIs. Multivariable logistic regression analysis was used to determine whether the development of AKI was associated with the antimicrobial combination treatment adjusting for baseline variables such as receipt of nephrotoxic agents, receiving antibiotics within 90 days, and Charlson Comorbidity Index (CCI). Nephrotoxic agents included nonsteroidal anti-inflammatory drugs, acyclovir, aminoglycosides, intravenous contrast, diuretics, amphotericin B, ACE inhibitors (ACE-I), angiotensin II receptor blockers, vasopressors, and intravenous chemotherapy. In addition, standardized inverse probability weighting (IPW) was used to reduce imbalance between combination treatment groups by removing measured confounders. A propensity score was calculated using logistic regression based on potential confounders of age, CCI, osteomyelitis, history of CKD, receiving antibiotic within 90 days, infectious diseases consultation, and having a history of penicillin allergy.[18] Calculations of stabilized inverse propensity scores as weights were used to analyze the development of AKI with a logistic regression model. Statistical analyses were performed using Stata for Windows V.16.0 (College Station, Texas) with statistical significance indicated by a p value of 0.05 and with the use of a two-sided hypothesis test.

Table 1 Baseline characteristics of patients receiving VAN+PTZ or VAN+CFP combination therapy

Characteristics	VAN+PTZ (n=140)	VAN+CFP (n=70)	P value
Mean age (years)±SD	54.9±11.3	60.0±10.4	0.014
Male n, (%)	99 (70.7)	41 (58.6)	0.078
Race n, (%)			0.949
White	74 (52.9)	37 (52.9)	
African American	63 (45.0)	31 (44.3)	
Other	3 (2.1)	2 (2.9)	
Mean weight (kg) ±SD	104.1±29.7	96.2±27.1	0.062
Mean hemoglobin A1c (%) ±SD**	9.5±2.7	9.3±2.4	0.759
Chronic kidney disease			0.503
Stage 2 n, (%)	3 (2.1)	1 (1.4)	
Stage 3 n, (%)	19 (13.6)	12 (17.1)	
Stage unknown n, (%)	12 (8.6)	7 (5.0)	
Median SCr (mL/min) at antibiotic initiation (IQR)	1.10 (0.90–1.49)	1.06 (0.77–1.51)	0.434
Mean Charlson Comorbidity Index ±SD	3.75±1.6	4.2±1.5	0.042
Primary admission service: ICU n, (%)	9 (6.4)	3 (4.3)	0.755
Sepsis criteria n, (%)	11 (7.9)	5 (7.1)	>0.999
Hypotension on admission n, (%)	26 (18.6)	8 (11.4)	0.185
Osteomyelitis n, (%)	99 (70.7)	38 (54.3)	0.018
Beta-Lactam or vancomycin in past 90 days n, (%)	31 (22.1)	23 (32.9)	0.094
Vancomycin loading dose given n, (%)	44 (31.4)	19 (27.1)	0.523
Mean vancomycin loading dose (mg/kg) ±SD	19.0±3.9	18.2±2.6	0.405
Mean vancomycin trough (mg/L) prior to AKI±SD	26.1±10.6	30.5±6.1	0.367
Nephrotoxic agent within 72 hours n, (%)	107 (76.4)	48 (68.6)	0.383
Number of nephrotoxic agents			0.154
One n, (%)	67 (47.9)	25 (35.7)	
Two to three n, (%)	22 (15.7)	14 (20.0)	
Three or more n, (%)	14 (10.0)	9 (12.9)	
Infectious diseases consult n, (%)	98 (70.0)	38 (54.3)	0.025
Nephrology consult n, (%)	27 (19.3)	2 (2.9)	0.001
Pharmacy pharmacokinetic consult n, (%)	138 (98.6)	65 (92.9)	0.043

**n=202 (PTZ n=133 and CFP n=69).
AKI, acute kidney injury; ICU, intensive care unit; SCr, serum creatinine.

RESULTS

Among 356 patients screened for inclusion, 210 were analyzed. Seventy patients were included in the VAN+CFP group and 140 in the VAN+PTZ group. Main reasons for exclusion were CKD ≥4 (32%), received >24 hours of either CFP or PTZ before switching to the other agent (22%), and initiation of the combination >24 hours apart (10%). Baseline demographics can be seen in table 1.

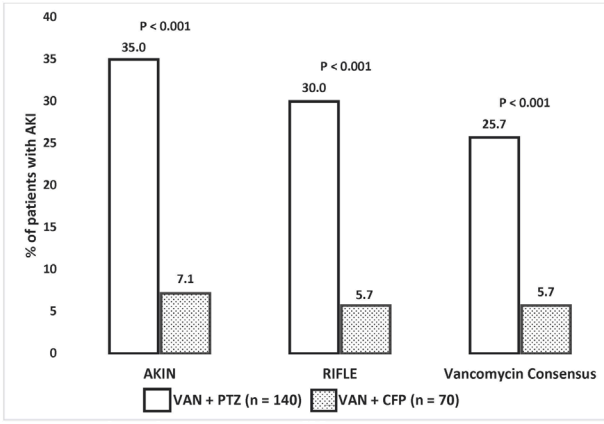

Figure 1 Rates of acute kidney injury (AKI) in VAN+PTZ vs VAN+CFP combination therapy. n=140 for the VAN+PTZ group and n=70 for the VAN+CFP group. Both treatment groups received at least 48 hours of the antibiotic combination therapy. AKIN, Acute Kidney Injury Network.

Differences were noted in characteristics between groups including age, CCI, diagnosis of osteomyelitis, and inpatient consult services (nephrology, infectious diseases, and vancomycin pharmacokinetic monitoring). Overall, patients receiving VAN+PTZ were more likely to develop AKI. Forty-nine of 140 patients (35%) in the VAN+PTZ group and 5 of 70 patients (7%) in the VAN+CFP group developed AKI according to the AKIN criteria (OR 7.00 (95% CI 2.64 to 18.53), p<0.001). The breakdown of AKI severity can be seen in figure 1. After adjusting for differences in CCI, antibiotics within 90 days, and the receipt of nephrotoxic agents, VAN+PTZ was an independent predictor of AKI (adjusted OR (aOR) 6.21; 95% CI 2.30 to 16.72; p<0.001). In the IPW analysis, there was a significant increase in the odds of developing AKI in the VAN+PTZ versus VAN+CFP group (aOR 7.47; 95% CI 2.57 to 21.68; p<0.001). Median time to developing AKI was 102.1 hours (IQR 47–152.7 hours) in the VAN+PTZ group versus 78.3 hours (IQR 39.8–100.6 hours) in the VAN+CFP group, which was not statistically significant (log-rank test p>0.999).

In the VAN+PTZ group, median length of stay was significantly prolonged at 11.9 days (IQR 7.9–17.8 days) versus 7.8 days (IQR 4.9–12.1 days) in the VAN+CFP group (p<0.001). VAN+PTZ was also associated with higher total hospital charges at US$99,742.83 (IQR US$69,342.50–US$165,549.59) compared with US$74,260.25 (IQR US$48,446.88–US$107,396.99) in the VAN+CFP arm (p<0.001).

DISCUSSION

DFIs are often managed with prolonged durations of broad-spectrum antimicrobial therapy.[1] Although drug-induced nephrotoxicity has been associated with VAN+PTZ therapy, the risk of AKI in patients treated for DFI is not well studied. Moenster *et al* demonstrated that treatment with VAN+PTZ for osteomyelitis in diabetic patients resulted in an increased risk of AKI when compared with treatment with VAN+CFP (OR 3.45; 95% CI 0.96 to 12.4; p=0.057). Although these results were not statistically significant, the study (n=139) did not meet their 400 patient enrollment goal. In addition, patients with stage 3 CKD or higher were excluded.[9] More recent studies have established the risk of nephrotoxicity of VAN+PTZ in hospitalized patients. Gomes *et al* evaluated the incidence of AKI in adult inpatients and found a significantly higher rate of AKI in the VAN+PTZ group (34.8%) compared with the VAN+CFP group (12.5%) in an unmatched analysis (OR 3.74; 95% CI 1.89 to 7.39; p<0.001).[7] Similar findings were concluded in a retrospective study conducted by Navalkele *et al*. The authors concluded that VAN+PTZ was an independent predictor for AKI (HR 4.27; 95% CI 2.73 to 6.68) in a multivariate analysis.[8]

Most of the previously mentioned studies, with the exception of Moenster *et al*, examined a diverse patient cohort and have demonstrated an increased risk of AKI with a VAN+PTZ combination. The intent of our study was to refocus on a diabetic patient population that may have the highest baseline risk for the development of drug-induced AKI in order to determine if this population would have a greater benefit of avoiding VAN+PTZ combinations. We performed logistic regression in an attempt to decrease bias and account for potential confounders. The unadjusted (OR 7.00; 95% CI 2.64 to 18.53) and adjusted (aOR 6.21; 95% CI 2.30 to 16.72) ORs are similar, which suggests the association is not attributed to confounding. This was also evident with IPW finding, improving the balance within each of the groups, suggesting the potential causal effect of VAN+PTZ and AKI. While we confirmed a high rate of AKI in patients receiving VAN+PTZ, we found lower rates of renal toxicity in CFP-treated patients in our study population when compared with previous literature, despite this group having higher CCI scores than the PTZ group. Nevertheless, this diabetic cohort demonstrated similar rates of AKI when compared with a previous all-inclusive cohort study at our institution with limited number of diabetic patients and those treated for skin and skin structure infections.[7] This evaluation provides original published evidence of a difference in rates of AKI between these two common antibiotic regimens in diabetic patients without excluding severe baseline renal insufficiency or recipient of nephrotoxic agents.

This study had several limitations. The data were retrospectively obtained from the electronic medical record in an unblinded manner, assuming accurate documentation. Through the use of logistic regression, we were able to account for differences in baseline covariates; however, there is the possibility of remaining unobserved confounding variables. While data were collected for risk factors predisposing patients to drug-induced AKI (eg, treatment with vasopressors, presence of hypotension or sepsis, CCI, receipt of other nephrotoxic agents), data were not collected to categorize the type of AKI (eg, direct nephrotoxicity vs acute interstitial nephritis).

In our study, we assessed incidence of AKI by collecting serum creatinine data. While creatinine is an established surrogate endpoint, this value may be influenced by extrarenal factors (eg, hydration status, muscle mass) and change in creatinine is delayed in relation to actual injury.[15 16] In addition, patients who received more than 24 hours of VAN+PTZ before switching to VAN+CFP were excluded from our study. It is possible that providers opted to switch

patients to VAN+CFP based on the anticipation or observation of AKI with VAN+PTZ. Thus, our study did not capture the risk of AKI in patients who switch from one regimen to another.

In conclusion, the use of the combination of VAN+PTZ appeared to be an independent risk factor for AKI in patients treated for DFI. In addition, the combination was associated with increased length of stay and higher hospital charges. Our findings imply that cefepime could represent a safer alternative to piperacillin–tazobactam when used in combination with vancomycin to treat DFI. While the current DFI guidelines do not provide recommendations for or against specific agents and the exact mechanism of AKI is unknown, our results suggest that VAN+CFP may be a preferred empiric regimen in this particularly vulnerable population on the basis of tolerability, length of stay, and hospital charges.[1]

Correction notice This article has been corrected since it first published. The provenance and peer review statement has been included.

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Correction: *Comparison of acute kidney injury in patients prescribed vancomycin in combination with piperacillin–tazobactam or cefepime for diabetic foot infections*

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