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Concerning Nephrotoxicity of Top Guns: Concomitant Pippercillin-tazobactam and Vancomycin with Vancomycin Alone During Treatment of Critically Ill Patients

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Abstract

Aim: Use of combination antibiotics piperacillin-tazobactam (PTZ) and vancomycin (VAN) is so often used as "top guns" for severe infections in hospitalized patients. VAN's nephrotoxicity is well-known. PTZ has been seen to prolong increased creatinine levels. Reports have surfaced higher rates of acute kidney injury (AKI) among patients treated with combination of PTZ + VAN in the literature. The purpose of this study was to compare the prevalence of AKI with the use of VAN alone and combination of PTZ + VAN treatment at our institution. Our hypothesis was that the combination of PTZ + VAN would be associated with higher prevalence of AKI compared with VAN only.

Materials and Methods: We performed this study to compare the combination of PTZ + VAN and VAN alone in critically ill patients in our hospital from 2016 to 2018. Included patients were stratified by treatment with PTZ + VAN and VAN alone.

Results: A total of 113 patients were included who were treated with PTZ + VAN and VAN alone. Patient demographics, comorbidities, sites of infection, and duration for 48 hours were compared. We found that PTZ + VAN was better than VAN alone in terms of AKI.

Conclusion: The combination of VAN plus PTZ is better use to prevent AKI over VAN monotherapy. Further research in the critically ill population is needed. Recent literature has suggested that the concomitant use of PTZ and VAN is associated with a higher risk of AKI compared with the use of VAN alone. Our study suggested that patients getting combination therapy were sicker hence receiving it as an empiric therapy and it is required to look at the possibility of residual confounding in previous studies.

Keywords: Acute kidney injury, vancomycin, pipercillin-tazobactam

Introduction

Toxic effects caused by antibiotics lead to altered intra-glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy (1). There is a limited published data available on evaluation of prevalence of acute kidney injury (AKI) in the co-administration of piperacillin-tazobactam (PTZ) and vancomycin (VAN). With such prevalent and increasing use of these antibiotic combinations, (2) especially in the emergency department (ED), it is vital to determine any potential for drug-induced comorbidities. It will help develop a thought process among emergency physicians before administrating antibiotics to keep in mind certain essential components such as avoiding further harm, safeguarding patient safety, reducing length of stay in hospital leading to reduced hospital cost. Therefore, we aim to evaluate and compare the prevalence of AKI within 48 hours of completion of therapy with concomitant PTZ and VAN with VAN alone in critically ill patients of an ED of a tertiary care hospital in Karachi, Pakistan.

Aims and Hypothesis

Specific Aim: The primary aim of this study was to find prevalence of AKI, within 48 hours of completion of therapy of concomitant PTZ and VAN versus VAN alone amongst critically ill patients,

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where antibiotics were initiated in the emergency room followed by ward admission in our hospital.

Secondary aims included AKI severity and time to AKI with outcomes such as length of stay and mortality.

Specific Hypothesis: Among adult patients there will be an increased prevalence of AKI within 48 hours of therapy with PTZ and VAN versus those treated with VAN alone.

Materials and Methods

Study Design

This was a retrospective cross sectional single-center study in critically ill patients admitted to a tertiary care hospital. Critically ill patients with sepsis who received VAN alone and those received combination therapy were identified from hospital's electronic medical records. Patients with normal renal function were defined as having an estimated glomerular filtration rate >60 mL/min. Patients received PTZ at a daily dose of 4.5 gram intravenously every 8 hours, and VAN 1 gram every 12 hours. Patients aged ≥18 years who had received a minimum of 48 hours of antibiotic treatment and who had a baseline serum creatinine (SCr) level measured within 24 hours of admission and whose SCr levels were checked daily or every other day, were included. An increase of ≥50% in SCr level from baseline or an absolute increase of ≥0.3 mg/dL in SCr level during antibiotic therapy or in the 72 hours after discontinuation of treatment would be considered AKI (2-10).

Study Duration: The data of past 1 year (January 2016 - December 2018) were collected to understand the trends and consequences of antibiotic use in this population.

Study Setting: Retrospective review of records of patients presenting to the ED.

Eligibility Criteria

- **Inclusion Criteria:**

1. All adult patients aged 18 years and older who were admitted in ED with sepsis. File codes for review: Sepsis and AKI
2. Initiation of concomitant therapy for 48 hours with an order for PTZ and VAN or VAN
3. Baseline SCr analyzed within 24 hours of admission
4. Patients with combination therapy if the PTZ was started within 48 hours of VAN

- **Exclusion Criteria:**

1. Patients on combination therapy already prior to ED visit
2. End stage renal disease or having a baseline raised SCr >1.5 mg/dL
3. Patients receiving hemodialysis or renal replacement therapy
4. Presence of shock
5. Mechanical ventilation
6. Chronic Liver disease
7. All pregnant women and patients having any history of an allergic reaction against a beta-lactam drug

Data Collection Procedure: A data collector was appointed who reviewed the electronic medical records system for all eligible adult patients presenting to the ED. All baseline socio-demographics (age, gender), suspected source of infection (skin and soft tissue infection, respiratory tract infection, intra-abdominal infection, urinary tract infection, empiric therapy, endocarditis, central nervous system infection, bone and joint infection, neutropenic fever) and SCr level measured in ED visit were be noted. The cases were divided into two groups as receiving PTZ and VAN or VAN alone.

Sample Size Calculation

An anticipated sample size of minimum 60 patients in VAN alone and 53 patients in PTZ + VAN were included rendering the total sample to be 113. Sample size was calculated by using OpenEpi software. The confidence interval was set to 95% with statistical power of 80% based on the estimates of a 41.3% rate of AKI in the PTZ + VAN and 15.7% in the VAN alone (3).

Patients from a sample in the PTZ + VAN group were consecutively selected from the most recent administration date until the minimum number of patients needed to meet the required sample size were included.

Ethical Review Committee Approval: The study was granted an exemption from the Ethical Review Committee of the Aga Khan University before initiation. All of the data collected remained confidential and properly stored as ethics review committee guidelines at the institution suggested. ERC approval granted by the Aga Khan University (protocol no: 2019-0880-2235).

Statistical Analysis

SPSS for Windows version 25.0 was used for statistical analyses. Variables were analyzed using Shapiro-Wilk test for their normality distribution where $p>0.05$ was taken as significant for normal distribution of data. Data were presented as mean ± standard deviation for continuous normally distributed variables while, continuous skew-distributed variables were presented as median (interquartile-range). Non-continuous variables were shown as numbers and frequencies. Univariate analyses were performed with χ^2 and Mann-Whitney U tests to identify variables.

Results

A record of 113 patients in total was selected for our retrospective analysis study. Almost half of them received PTZ + VAN (53/113; 46.9%). Age and gender distribution were almost equal among the groups (Table 1). Every patient who received the combination of PTZ + VAN had sepsis while only two-third of the patients who received VAN alone had sepsis. Hypertension was the most common comorbidity found in both the groups followed by Diabetes Mellitus. One-third of the patients in both the groups had their primary infective source within lung which was the major chunk of our selected patients. Patients treated with PTZ + VAN had higher exposure to other potential nephrotoxic drugs compared with VAN alone group with loop diuretic being the most common drug concomitantly taken by the overall population of our patients (35/113). Exposure to antibiotics other than PTZ and VAN was highest (34%) in our PTZ + VAN group. Median duration of antibiotic therapy was significantly higher in the PTZ + VAN group compared with VAN alone group [84 vs 36 hours, (U=1024, p=0.001)]. In the entire group of our sample population, AKI developed in 46 patients (40.6%) which was significantly higher in the VAN alone (53.3%) $\chi(1) = 8.448$, p=0.004 compared with PTZ + VAN group (26.4%). In the comparison of AKI between PTZ + VAN and VAN alone group (Table 2), it was observed that time taken for AKI development was almost equal in both the groups, but time taken for resolution was longer in VAN alone group. According to Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease staging, AKI developing in VAN alone

Table 1. Demographics and comparison between piperacillin-tazobactam + vancomycin and vancomycin groups

	PTZ + VAN (n=53)	VAN (n=60)	p
Age, years (mean +/- SD)	53.68 +/- 20.08	55.60 +/- 20.31	-
Gender			
Male (%)	31 (58.5%)	34 (56.7%)	-
Female (%)	22 (41.5%)	26 (43.3%)	-
Sepsis (%)	53 (100%)	37 (61.6%)	-
Comorbidities			
HTN (%)	20 (37.7%)	26 (43.3%)	-
DM (%)	17 (32%)	19 (31.6%)	-
CKD (%)	0 (0%)	3 (5%)	-
Source			
Lung (%)	18 (34%)	22 (36.6%)	-
Urinary Tract (%)	5 (9.4%)	6 (10%)	-
CNS (%)	3 (5.6%)	9 (15%)	-
Intra-abdominal sepsis (%)	4 (7.5%)	7 (11.6%)	-
Endocarditis (%)	0 (0%)	4 (6.6%)	-
Osteomyelitis (%)	2 (3.7%)	2 (3.3%)	-
Necrotizing fasciitis (%)	4 (7.5%)	1 (1.6%)	-
Diabetic foot (%)	3 (5.6%)	0 (0%)	-
Febrile neutropenia (%)	3 (5.6%)	0 (0%)	-
Other infection (%)	7 (13.2%)	2 (3.3%)	-
Unknown (%)	7 (13.2%)	14 (23.3%)	-
Duration of antibiotic therapy, hours (median; range)[a]	84; 24-144	36; 24-72	**0.001**
Other drugs (%)	35 (66%)	39 (65%)	-
NSAIDs (%)	11 (20.7%)	6 (10%)	-
Loop diuretic (%)	12 (22.6%)	23 (38.3%)	-
ACEI (%)	1 (1.8%)	1 (1.6%)	-
ARBS (%)	5 (9.4%)	1 (1.6%)	-
Amphotericin B (%)	1 (1.8%)	3 (5%)	-
Acyclovir (%)	2 (3.7%)	5 (8.3%)	-
Other antibiotics (%)	18 (34%)	6 (10%)	-
Total hospital stay, hours (median; range)[a]	144; 96-240	120; 84-216	0.546
Development of AKI (%)[b]	14 (26.4%)	32 (53.3%)	**0.004**

PTZ: Piperacillin-tazobactam, VAN: Vancomycin, HTN: Hypertension, DM: Diabetes Milletus, CKD: Chronic Kidney disease, CNS: Central nervous system, NSAIDs: Non-steroidal Anti-inflammatory drugs, ACEI: Angiotensin converting enzyme inhibitors, ARBS: Angiotensin II receptor blockers, AKI: Acute kidney injury, [a]: Mann-Whitney U test, [b]: chi-square test, *: Bold values indicate statistically significant difference (p<0.05), SD: Standard deviation

Table 2. Comparison between the characteristics of kidney injury in piperacillin-tazobactam + vancomycin and vancomycin groups

	PTZ + VAN (n=14)	VAN (n=32)	p
Time to development of AKI, hours (median; range)[a]	48; 24-96	48; 24-72	0.449
AKI stage[b]	-	-	0.355
Risk (%)	7 (50%)	7 (21.9%)	-
Injury (%)	4 (28.6%)	13 (40.6%)	-
Failure (%)	3 (21.4%)	9 (28.1%)	-
Loss (%)	0 (0%)	1 (3.1%)	-
ESRD (%)	0 (0%)	2 (6.2%)	-
Outcome[b]	-	-	0.055
Resolved (%)	5 (35.7%)	8 (25%)	-
Persisted (%)	3 (21.4%)	19 (59.4%)	-
Mortality (%)	6 (42.9%)	5 (15.6%)	-
Time to resolution, hours (median; range)[a]	48; 24-216 (n=5)	120; 54-180 (n=8)	0.416
Total hospital stay, hours (median; range)[a]	192; 114-288	144; 90-216	0.288

PTZ: Piperacillin-tazobactam, VAN: Vancomycin, AKI: Acute kidney injury, ESRD: End Stage Renal disease, [a]: Mann-Whitney U test, [b]: chi-square test

group was of higher stage compared with PTZ + VAN group and while AKI persisted more frequently in the VAN alone group, the mortality rate was higher in the PTZ + VAN group. However, the thing to take notice was, none of these differences between PTZ + VAN and VAN alone group was statistically significant as evident by "p-values" presented in the table. Our secondary finding showed that patients with concomitant exposure to loop diuretic had significantly higher incidence of AKI compared with patients without exposure to loop diuretic [65.7% vs 29.5% ($\chi(1) = 13.136$, $p<0.001$] AKI developing in only 29.5% of the patients who did not receive loop diuretic.

Discussion

Our study showed that the incidence of AKI was significantly higher in the VAN only group (41.3%) compared with the PTZ + VAN group (16.0%). Davies et al. (1) focused on the combination of PTZ and VAN and reinforced our findings in their study. Jensen et al. (2) meticulously evaluated the effects of PTZ on renal function which was the re-analysis of data from a 1200-patient multicenter clinical trial and showed that patients treated with PTZ exhibited delayed improvement in their SCr during antibiotic therapy, compared with patients treated with meropenem (2-4). Our study set up a match between the veterans (VAN with well-known renal toxicity) and upcoming qualifier PTZ. However, it should be highlighted that VAN-associated renal toxicity really depends on the filtration system of kidney's function.

It was considered that PTZ raised the SCr without harming the kidneys. PTZ reduces creatinine secretion via organic anion transport system which is defined as "pseudo-nephrotoxicity" and recent studies (5-9) doesn't show acute renal damage. Some studies shows that combination antibiotics might even have a nephron-protective effect (9) and further studies are needed to show the clear evidence.

Literature findings suggested that critically ill patients at the time of ED presentation were very sick and that nephrotoxicity should be kept in mind before giving antibiotics (10-12). It is hard to label combination antibiotics as nephrotoxic but it's important to deliberate when to choose the top guns to avoid further morbidity and mortality and increased financial burdens in terms of prolonged hospital stay.

Knowing the physiology, VAN causes oxidative injury while many risk factors such as preexisting renal disease, hypotension, obesity, hospitalization in critical care unit are already in play. VAN, being a favorite antibiotic for many physicians, requires rigorous pharmacy insights for its therapeutic dosing and serum level monitoring.

Study Limitations

Limitation of this study is its retrospective design and potential confounding by indicating the risk of overfitting when selecting variables for regression based on a univariate analysis and finally, the large number of predictors with respect to the numbers of observation (12). The large majority of studies supporting higher incidence of AKI in patients receiving PTZ + VAN compared with VAN alone are based on retrospective data. Nevertheless, it is said that there is no smoke without fire and considering this a potential modifiable risk factor for AKI, further research is certainly warranted. No studies in Pakistan is yet performed which have closely looked into the association of empiric antimicrobial therapies with an increased risk for AKI, which would be a much more clinically important and relevant finding. This was a retrospective single-center study and should be considered hypothesis-generating and literature review with local data set in a different set of population at best.

Conclusion

PTZ toxicity is an emerging situation with a clinical impact that is just now being increasingly recognized and appreciated. Studies stating combination of PTZ + VAN causing AKI are certainly not enough to demonstrate causation, but it is an interesting association nonetheless. Nevertheless, the study findings should encourage physicians to take the usual care in dosing PTZ and VAN with close serum VAN monitoring especially in patients receiving the combination. Antibiotics should be de-escalated as soon as feasible, such as discontinuing VAN if methicillin-resistant staphylococcus aureus is not a serious concern. Following procalcitonin levels, along with blood culture results, leukocytosis and temperature curves, can help us give physicians confidence in safely discontinuing or narrowing antibiotics.

Ethics

Ethics Committee Approval: The study was granted an exemption from the Ethical Review Committee of the Aga Khan University before initiation. (protocol no: 2019-0880-2235)

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practice: Concept: Design: Data Collection or Processing: S.S., M.A.S., M.S.K., U.J., M.S.K., Analysis or Interpretation: M.A.S., M.S.K., Literature Search: Writing: M.A.B, M.S.K.

Conflict of Interest: None declared.

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