Risk of Acute Kidney Injury in Patients Treated with Vancomycin and Piperacillin/Tazobactam Compared to Vancomycin and Meropenem or Doripenem: A Retrospective Cohort Study

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It has been reported that the risk of acute kidney injury (AKI) is higher during treatment with vancomycin and piperacillin/tazobactam compared to use of vancomycin and cefepim or meropenem. We investigated the risk of AKI in patients receiving vancomycin and piperacillin/tazobactam versus those receiving vancomycin and meropenem or doripenem. The subjects were patients over 18 years old who received either vancomycin and piperacillin/tazobactam (V+P/T therapy) or vancomycin and carbapenems (meropenem or doripenem) (V+C therapy) for at least 48 h between 1 May 2013 and 28 February 2019. The primary endpoint was the incidence of AKI in patients receiving V+P/T or V+C therapy, while the secondary outcome was the timing of AKI in each group. The incidence of AKI was 33.3% (9/27) in patients receiving V+P/T therapy versus 9.1% (5/55) in those receiving V+C therapy, and its incidence was significantly higher with the former regimen (χ² = 5.90, p = 0.015). Multiple logistic regression analysis confirmed that V+P/T therapy was associated with an increased risk of AKI compared to V+C therapy (adjusted odds ratio: 5.05, 95% confidence interval: 1.46–17.5, p = 0.01). The time to onset of AKI after initiation of treatment was not significantly different between patients receiving V+T/P or V+C therapy [median (interquartile range): 4 d (2–6 d) versus 7 d (3–10 d); p = 0.282]. V+P/T therapy was associated with a significantly higher incidence of AKI than alternative regimens, suggesting that it should be avoided. When broad spectrum antibacterial therapy is required, V+C therapy should be considered instead.

Key words—vancomycin; piperacillin/tazobactam; acute kidney injury; meropenem; doripenem

INTRODUCTION

Vancomycin is the first-line antimicrobial agent for infections caused by methicillin-resistant Staphylococcus aureus. Piperacillin/tazobactam has a broad spectrum of activity against gram-positive bacteria, anaerobes, and gram-negative bacteria, including Pseudomonas aeruginosa, and it is widely used to treat febrile neutropenia as well as urinary tract infections or other infections. Meropenem and doripenem are carbapenems that are also employed to treat infections requiring broad-spectrum coverage. Vancomycin is occasionally combined with antipseudomonal antibiotics such as piperacillin/tazobactam or carbapenems as empirical therapy when the cause of a severe infection is unknown. However, renal dysfunction is a well-known adverse effect of vancomycin,1 and it was recently reported that the risk of acute kidney injury (AKI) is increased when vancomycin is combined with piperacillin/tazobactam.2-7 Three investigations have identified a higher risk of AKI in patients treated with vancomycin and piperacillin/tazobactam than in those receiving vancomycin and cefepim.8-10 There have also been two reports that the risk of AKI is higher in patients treated with vancomycin and piperacillin/tazobactam compared to those receiving vancomycin and meropenem.11,12 However, no information is available about the risk of AKI in adult patients on treatment with vancomycin and piperacillin/tazobactam versus vancomycin and meropenem or doripenem. Therefore, we investigated the incidence of AKI in adult Japanese patients receiving combined therapy with vancomycin and piperacillin/tazobactam versus those receiving vancomycin and meropenem or doripenem.

METHODS

This study was approved by the ethics committee of Chutoen General Medical Center (approval No. 64) and was performed in conformity with the Declaration of Helsinki. We performed a single-center, retrospective cohort study of patients over 18 years old admitted to our Medical Center between 1 May 2013 and 28 February 2019 who received treatment...
for at least 48 h with either vancomycin and piperacillin/tazobactam (V + P/T) or vancomycin and a carbapenem (meropenem or doripenem) (V + C). According to published product information (package insert), AKI has been reported in 1.9% of patients receiving meropenem and 1.0% of patients treated with doripenem. Therefore, we considered that data on meropenem and doripenem could be combined as a carbapenem group for the present analysis. Patients were excluded if there was no information on their body weight or baseline serum creatinine (S-Cr), and if they were on hemodialysis. Patients admitted to the intensive care unit (ICU) were also excluded, since it has been reported that AKI associated with vancomycin therapy is more frequent among patients receiving intensive care.13

The primary endpoint of this study was the incidence of AKI in the patients receiving V + P/T therapy (V + P/T group) versus those receiving V + C therapy (V + C group). According to the Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, AKI was defined as an increase of S-Cr by ≥0.3 mg/dL within 48 h or an increase of S-Cr to ≥1.5 times the baseline value that was known/presumed to have occurred within the previous 7 d.14 Creatinine clearance (Ccr) was calculated by the Cockcroft-Gault formula.15 When the blood concentration of vancomycin was measured, a trough sample was obtained before the third to fifth vancomycin infusion. According to previous reports,16-18 high-dose therapy was defined as ≥3 g of meropenem or doripenem daily, or as ≥18 g of piperacillin/tazobactam daily. The secondary outcome was the timing of the onset of AKI in each group.

Statistical Analysis Nominal variables were compared by the χ² test. Continuous variables were initially analyzed by the Kolmogorov-Smirnov test to assess the normality of their distribution. Student’s t-test or one-way ANOVA was performed for parametric data, while the Mann-Whitney U test or the Kruskal-Wallis test was used to compare non-parametric data. Multiple logistic regression analysis was performed using risk factors showing a high prevalence in a previous study19 (concomitant use of diuretics or vasopressors) and potential risk factors identified by univariate analysis in this study (p < 0.1). In all analyses, p < 0.05 was accepted as indicating statistical significance. Analyses were conducted with EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama), a graphical user interface for R (The R Foundation for Statistical Computing).20 The sample size for this study was calculated using the “Power and Sample Size Calculation” program, version 3.1.2.,21 by assuming a frequency of 10% for the risk of AKI in the V + C group and an α value of 0.05, along with 80% power to detect associations with the risk of AKI at an odds ratio of 5.0. It was calculated that a total of 90 patients was needed (30 patients in the V + P/T group and 60
patients in the V + C group).

RESULTS

During the study period, 155 patients received V + P/T or V + C therapy for at least 48 h. Among them, 73 patients met the exclusion criteria and the remaining 82 patients were analyzed (Fig. 1). In the V + C group \( n = 55 \), 49 patients received vancomycin and meropenem, while 6 patients who received vancomycin and doripenem. Among the baseline characteristics of the V + P/T group and the V + C group, only high-dose therapy showed a significant difference (Table 1). Other characteristics did not differ significantly. The incidence of AKI was 33.3\% (9/27) in the V + P/T group versus 9.1\% (5/55) in the V + C group, and the incidence was significantly higher in the V + P/T group \( (\chi^2 = 5.90, p = 0.015) \). Overall, AKI occurred in 17.1\% (14/82) of all patients. When baseline characteristics were compared between patients with and without AKI in the V + C group and the V + P/T group (Table 2), no potential risk factors for AKI \( (p < 0.1) \) were identified. Among patients with AKI, the median increase of S-Cr was 1.6-fold in the V + C group versus 1.9-fold in the V + P/T group \( (p = 0.44) \). Vancomycin trough concentrations were measured in 72 out of 82 patients (V + C group, 48/55; V + P/T group, 24/27), and the trough concentration was \( > 15 \mu g/mL \) in 37 patients (V + C group, 25/48; V + P/T group, 12/24). The influence of concomitant medications (diuretics and vasopressors) on the incidence of AKI was investigated by multiple logistic regression analysis, along with V + P/T therapy and V + C therapy. This analysis revealed that V + P/T therapy was associated with an increased risk of AKI compared to V + C therapy (adjusted odds ratio: 5.05, 95\% confidence interval: 1.46–17.5, \( p = 0.01) \).

The median time to the onset of AKI was 4 d \( [\text{interquartile range (IQR): 2–6 d}] \) in the V + P/T group compared with 7 d \( [\text{IQR: 3–10 d}] \) in the V + C group, showing no significant difference between the two groups \( (p = 0.282) \).

DISCUSSION

It has already been reported that the incidence of AKI is higher in patients receiving vancomycin and piperacillin/tazobactam than in those receiving vancomycin and meropenem,\(^{1,12}\) but there has been no information available about the risk of AKI in patients on treatment with vancomycin and piperacillin/tazobactam versus vancomycin and carabepenems (including doripenem). In agreement with previous reports, we found a significantly higher incidence of AKI in patients receiving V + P/T therapy compared to those on V + C therapy. In the V + C group, there was no significant difference of AKI risk between patients treated with vancomycin and meropenem or vancomycin and doripenem \( [4/49 (8.2\%) \text{ vs. 1/6 (16.7\%)} , p = 1.0) \). Since there is not much difference in the risk of AKI between meropenem and doripenem according to the published product information, we considered that data on these carabepenems could

| Table 1. Clinical Profile of the V + C and V + P/T Groups |
|---|---|---|---|
| Group | V + C | V + P/T | p value |
| No. of patients | 55 | 27 |
| Age | 70.7 ± 16.4 | 73.4 ± 14.4 | 0.47 |
| Body weight | 50.4 ± 12.2 | 51.9 ± 13.8 | 0.62 |
| Gender (male/female) | 40/15 | 15/12 | 0.19 |
| Baseline S-Cr (mg/dL) | 1.00 ± 0.62 | 0.92 ± 0.41 | 0.53 |
| Baseline Ccr (mL/min) | 62.4 ± 36.7 | 62.7 ± 35.9 | 0.97 |
| Vancomycin dose > 4 g/d | 3 (5.5) | 0 | 0.54 |
| High-dose therapy* | 26 (47.3) | 1 (3.7) | < 0.01 |

Concomitant medications

Diuretics | 12 (21.8) | 9 (33.3) | 0.39 |
Vasopressors | 4 (7.3) | 4 (14.8) | 0.49 |
NSAIDs | 11 (20.0) | 6 (22.2) | 1.0 |
ACE inhibitors/ARBs | 8 (14.5) | 5 (18.5) | 0.75 |
Amphotericin B | 1 (1.8) | 1 (3.7) | 1.0 |
TMP/SMX | 6 (10.9) | 5 (18.5) | 0.55 |
Comorbidities

Diabetes mellitus | 13 (23.6) | 6 (22.2) | 1.0 |
Malignancy | 24 (43.6) | 12 (44.4) | 1.0 |
Indication for antibiotics

Bacteremia | 4 (7.3) | 2 (7.4) | 1.0 |
Skin and soft tissue infection | 3 (5.5) | 1 (3.7) | 1.0 |
Respiratory tract infection | 12 (21.8) | 6 (22.2) | 1.0 |
Intra-abdominal infection | 7 (12.7) | 3 (11.1) | 1.0 |
Urinary tract infection | 8 (14.5) | 3 (11.1) | 0.93 |
Bone and joint infection | 4 (7.3) | 3 (11.1) | 0.87 |
Febrile neutropenia | 7 (12.7) | 7 (25.9) | 0.24 |
Meningitis | 5 (9.1) | 0 | 0.26 |
Empirical therapy | 3 (5.5) | 2 (7.4) | 1.0 |

Data show the number of patients (%) or the mean ± S.D. Nominal variables were compared by using the \( \chi^2 \) test. Student’s \( t \)-test was employed for normally distributed variables, while the Mann-Whitney \( U \) test was used for other variables. * High-dose therapy was defined as \( \geq 3 \) g of meropenem or doripenem daily, or as \( \geq 18 \) g of piperacillin/tazobactam daily. V + C, vancomycin + carbapenem; V + P/T, vancomycin + piperacillin/tazobactam; S-Cr, serum creatinine; Ccr, creatinine clearance; NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; TMP/SMX, trimethoprim/sulfamethoxazole.
be combined in the present study. Three previous studies have compared the risk of AKI between patients on V + T/P therapy and those receiving vancomycin combined with meropenem.\textsuperscript{11,12,22} In two of these studies, the risk of AKI was found to be higher with V + P/C therapy than with vancomycin and meropenem,\textsuperscript{11,12} while the other study showed no significant difference between the two regimens.\textsuperscript{22} Two of the three studies enrolled critically ill patients.\textsuperscript{11,22} It was reported that the frequency of AKI associated with vancomycin is higher among patients receiving intensive care,\textsuperscript{13} and it is problematic to compare critically ill patients with non-critically ill patients in relation to drug treatment, vital signs, and other factors. Accordingly, we excluded patients admitted to ICU from our study, as was done by Robertson \textit{et al.}\textsuperscript{12} It was reported that high-dose vancomycin therapy (≥ 4 g/d) is associated with an increased risk of AKI,\textsuperscript{12,23} but we found no significant difference of AKI risk related to the dose of vancomycin in the present study. When we compared baseline characteristics between patients with and without AKI in the V + C group and the V + P/T group, we found no significant differences of factors that are thought to influence the blood level of vancomycin, including the age, body weight, S-Cr, and Ccr. It was previously reported that concomitant use of nephrotoxic agents and female sex are associated with a higher risk of AKI in patients on V + P/T therapy.\textsuperscript{4,6} But both of these factors were not significant in the present study.
Morimoto et al. reported that AKI was more frequent when piperacillin/tazobactam was administered at a dose of 4.5 g versus a dose of 2.25 g. However, 90.0% (9/10) of the patients with AKI and 94.1% (16/17) of the patients without AKI received a dose of 4.5 g in the V + P/T group, so the dose of piperacillin/tazobactam did not influence AKI risk in our study (p = 1.0).

There have been several reports that the time to onset of AKI is shorter in patients receiving V + P/T therapy than in those on V + C therapy or vancomycin combined with cefepim. In the present study, the time to onset of AKI was shorter in the V + P/T group than the V + C group, but there was no significant difference between them.

A number of studies have shown that a vancomycin trough concentration $\geq 15$ or 20 $\mu$g/mL is associated with an increased risk of AKI in patients on V + P/T therapy. In the present study, some patients discontinued V + P/T therapy before the trough concentration of vancomycin was measured due to rapid onset of AKI, but the trough concentration was $\geq 15$ $\mu$g/mL in all patients developing AKI who underwent measurement of the trough level. Irrespective of the use of concomitant drugs such as piperacillin/tazobactam, meropenem, or cefepim, it seems that a trough concentration of vancomycin $\geq 15$ $\mu$g/mL increases the risk of AKI, even when vancomycin is administered alone, as reported previously.

The patients in the present study were older and their body weight was lower than in previous reports. Even so, the risk of developing AKI was significantly higher in the V + P/T group compared with the V + C group (including patients treated with meropenem or doripenem), although the time to onset of AKI showed no significant difference between the two groups. We performed a retrospective cohort study at a single center, and the number of patients treated with vancomycin and doripenem was much smaller than the number receiving vancomycin and meropenem. The small sample size was considered to be the reason for the wide confidence interval. Accordingly, a larger prospective investigation will be required to clarify the risk of AKI in patients receiving concomitant therapy with vancomycin and piperacillin/tazobactam or vancomycin and carbapenems such as meropenem or doripenem.

In conclusion, V + P/T therapy was associated with a higher risk of AKI than V + C therapy in non-ICU adult patients, although the underlying mechanism is still unknown. These findings suggest that use of V + P/T therapy should be avoided, if possible. When broad-spectrum antibacterial therapy is required in patients with febrile neutropenia or other severe infections, concomitant use of vancomycin and meropenem or vancomycin and doripenem should be considered instead.

Conflict of Interest The authors declare no conflicts of interest.

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