Frequency of Acute Kidney Injury Caused by Tazobactam/Piperacillin in Patients with Pneumonia and Chronic Kidney Disease: A Retrospective Observational Study

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Tazobactam/piperacillin (TAZ/PIPC) is a combination antibiotic frequently used to treat pneumonia. It has recently been reported that TAZ/PIPC worsens renal function in patients with existing renal impairment. Creatinine clearance is generally between 10 and 40 mL/min in Japanese patients, so TAZ/PIPC is given at a dose of 2.25 g three times daily or 4.5 g twice daily. If pneumonia is severe or intractable, the dose frequency may be increased to 2.25 g four times daily and 4.5 g three times daily. We examined the effect of these different dosing regimens on renal function. We studied a cohort of 57 patients with impaired renal function hospitalized with pneumonia and treated with TAZ/PIPC between January 2015 and November 2016. Patients were classified into four groups according to TAZ/PIPC dose: 2.25 g three times daily (Group A); 2.25 g four times daily (B); 4.5 g twice daily (C) and 4.5 g three times daily (D). We examined the frequency of acute kidney injury (AKI) and treatment effectiveness. In Groups A, B, C and D, AKI occurred in 5.6 %, 0.0 %, 25.0 % and 38.5 % of patient. In groups C and D, hydration and dose reduction were required to address early signs of impending AKI. Our findings suggest that the higher TAZ/PIPC dose of 4.5 g was responsible for the decline in renal function, even if the dose frequency was reduced.

Key words—tazobactam/piperacillin; chronic kidney disease; acute kidney injury; administration method; Kidney Disease: Improving Global Outcomes

INTRODUCTION

Tazobactam/piperacillin (TAZ/PIPC) combines a β-lactamase inhibitor with a penicillin-based antibiotic at the ratio of 1:8. In Japan, TAZ/PIPC is licensed for use in pneumonia, sepsis, pyelonephritis, complex cystitis, peritonitis, abdominal abscess and cholecystitis. Piperacillin was first approved for use in 1979; it is effective against both Gram-positive and Gram-negative bacteria, as it acts to degrade the peptidoglycan structure of the bacterial cell wall.1,2) Tazobactam was developed in 1983; it inhibits β-lactamases, such as penicillinase and cephalosporinase, which penicillin-resistant bacteria produce. Tazobactam forms complexes with the β-lactamase to inhibit the action of these enzymes irreversibly, and endows PIPC with a broader spectrum of action. Consequently, TAZ/PIPC is used for intractable infections, for which there is a strict requirement for appropriate and correct administration.

The main adverse reactions of TAZ/PIPC are elevations of hepatic enzyme concentrations in the blood and diarrhea. Renal impairment is also listed as a potential but uncommon adverse reaction in the statement of product characteristics; the frequency of acute kidney disease provoked by TAZ/PIPC is reportedly 0.3 %. However, a growing number of studies have reported a higher frequency of renal disorders as an adverse reaction of TAZ/PIPC therapy.3–5) Jensen et al.5) reported renal disorders in a cohort of 1200 critical care patients treated with TAZ/PIPC, meropenem or cefuroxime. They used multivariable logistic regression to identify that treatment with TAZ/PIPC, Acute Physiology and Chronic Health Evaluation (APACHE) II score >20 and age >65 years was associated with a delayed recovery in estimated glomerular filtration rate (eGFR) compared with other β-lactamase inhibitors. Karino et al.4) reported that severe nephrotoxicity was induced by TAZ/PIPC in four out of a cohort of 22 elderly Japanese patients with healthcare-associated pneumonia (18.2 %), and that patients with a creatinine clearance (CCr) <40 mL/min were most at risk. Igarashi et al.5) reported that of 198 patients treated...
with TAZ/PIPC between 2010 and 2012, 12 (6.1%) experienced moderate or severe adverse reactions affecting renal function.

TAZ/PIPC comprises a penicillin-based antibiotic combined with a β-lactamase inhibitor, of which the common maximal dose is internationally established. Reports from overseas studies indicated that the half-life of this drug is extended in patients with impaired renal function.\(^6\) Additionally, the pharmacokinetics of TAZ/PIPC in such patients has been examined overseas,\(^7\) and evidence of its use has been accumulated.

For Japanese patients with impaired renal function, Shiba has recommended that TAZ/PIPC dosing should be adjusted in Japanese patients based on pharmacokinetic and the pharmacodynamic analyses.\(^8\) In Japanese patients with community-acquired pneumonia, population pharmacokinetic analysis was used to identify the ratio of the time at which the plasma PIPC concentration exceeded the minimum inhibitory concentration (MIC) to the dosing interval (proportion of time above MIC, %TAM), and identified that TAZ/PIPC should be administered at a dose of 2.25 g three times daily or 4.5 g twice daily in patients with a CCr between 10 and 40 mL/min.\(^9\) In both dosing regimens, the %TAM for patients with impaired renal function is equivalent to that of patients with normal renal function receiving 4.5 g three times daily. Additionally, for patients with very severe or intractable pneumonia and a CCr between 10 and 40 mL/min, the recommended doses are 2.25 g four times daily or 4.5 g three times daily, compared with 4.5 g four times daily in patients with normal renal function.

Nevertheless, the influence of these different dosing regimens on renal function has not been fully clarified. We examined the influence of these different TAZ/PIPC dosing regimens in Japanese patients with impaired renal function.

**MATERIALS AND METHODS**

We undertook a retrospective observational study at the Suita Tokushukai Hospital, Japan. Conduct of the study was approved by the hospital’s Ethics Review Committee for Clinical Research (approval number 10). We identified 60 ethnically Japanese patients with impaired renal function hospitalized with pneumonia and treated with TAZ/PIPC between January 2015 and November 2016. Three patients were excluded from the analysis as the antibiotics were changed immediately due to lack of sensitivity of the causative organism to TAZ/PIPC. The eGFR individualized for body surface area (eGFR-IND) was between 10 mL/min and 40 mL/min in all 57 patients. The half-life of TAZ of patients with eGFR between 10 and 40 mL/min is reported as 6 h. Then, patients treated TAZ/PIPC more than 3 d, 5 times the half-life were adopted, because their blood concentrations of TAZ were expected to become steady state. Patients were classified into one of four groups according to the TAZ/PIPC dosing regimen: Group A, 2.25 g three times daily; Group B, 2.25 g four times daily; Group C, 4.5 g twice daily; and Group D, 4.5 g three times daily. As described above, the regimens for Group B and Group D were endorsed for patients with very severe or intractable pneumonia.

The diagnosis of pneumonia, referring to the report of Miyashita et al.\(^10\) and Hoere et al.,\(^11\) was assessed. The following criteria (1) and (2) are essential conditions and two criteria out of the three criteria (3) to (5) are satisfied; (1) Invasive shadows are observed in chest X-ray infiltration before dosing; (2) Cough, sputum, respiratory symptoms such as dyspnea feeling; (3) Fever (≧37.5°C); (4) increasing of the white blood cell count to ≧10000/μL; (5) increasing of a serum C-reactive protein (CRP) concentration (≧10 mg/dL).

Disease severity was evaluated using the Sequential Organ Failure Assessment (SOFA) score.\(^12\) Additionally, serious case of pneumonia was judged, referring to the report of Kohno et al.,\(^13\) satisfy one of the following. (1) a resident of an extended care facility or nursing home, (2) a person who has been discharged from a hospital within in preceding 90 d, (3) an elderly or disabled person who is receiving nursing care, (4) a person who is receiving regular endovascular treatment as an outpatient (immunosuppressant therapy).

The frequency of renal disorders, treatment effectiveness, and serum Cr concentration (SCr), eGFR-IND and CCr before and after TAZ/PIPC administration, were compared between the groups. The expressions of eGFR-IND and CCr were as follows.

\[\text{eGFR-IND} = \text{eGFR-NOR} \times \text{body surface area} \]

\[\text{eGFR-NOR} \text{ (mL/min/1.73 m²)}\]
Male: eGFR-NOR (mL/min/1.73 m²) = 194 × SCr⁻¹.094 × age⁻⁰.₂₈⁷
Female: eGFR-NOR (mL/min/1.73 m²) = eGFR-NOR (mL/min/1.73 m²) of male×0.739

Body surface area = body weight⁰.₄₂₅ × height⁰.₇₂₅ × 0.₆₀₀₇₁₈₄

CCr (mL/min)
Male: CCr (mL/min) = ((140-age) × body weight) / (72 × SCr)
Female: CCr (mL/min) of male×0.₈₅

In addition, the treatment period of patients who were occurred acute kidney injury (AKI) was investigated.

Renal failure was assessed using the classification of Kidney Disease: Improving Global Outcomes (KDIGO) criteria,¹⁴ which define AKI as SCr ≥0.3 mg/dL within 48 h, or a 1.5-fold increase from the baseline value measured within the previous 7 d.

The effectiveness of TAZ/PIPC, referring to the report of Miyashita et al.,¹⁰ was assessed on the fourth day after the first dose, and again at the time of the last dose. It was judged to be effective if three or more of the following criteria were met: (1) reduction of the body temperature to <37°C; (2) restoration of the white blood cell count to <8000/μL or to within the normal range; (3) achievement of a serum CRP concentration 30% of that at the time of the first dose; (4) clear improvement of chest X-ray infiltration.

**Statistical Analysis**

Values are presented as the mean and S.D. Differences between the groups’ demographic and clinical characteristics were examined using the t-test. The Kruskal Wallis H-test was used to compare SOFA scores. The Mann-Whitney U test was used to compare the treatment periods. When the paired t-test was used to compare values before and after TAZ/PIPC therapy, Fisher’s exact test was used to compare the number of patients meeting the effectiveness criteria between two groups. Similarly, the likelihood ratio test was used in the four groups. p values <0.05 were considered statistically significant.

**RESULTS**

Patients’ demographic and clinical characteristics are shown in Table 1. In the mean SOFA disease severity score, there was not significantly difference. But the numbers of serious case of pneumonia, referring to the report of Kohno et al.,¹³ in Group B or D were greater than A or C. The eGFR-IND and CCr were significantly lower in Group A than Group C. And there was no significant difference in serum sodium concentration between the groups, suggesting that there was no difference in hydration status.

The incidence of AKI in each group according to the KDIGO definition is shown in Table 2. In Group A (2.25 g three times daily) and Group C (4.5 g twice daily), AKI occurred in 5.6% and 25.0%, respectively, but this difference was not statistically significant. However, the incidence of AKI was significantly higher in patients with very severe or intractable pneumonia receiving higher doses: the incidence in Group D (4.5 g three times daily) was 38.5%, compared with 0% in Group B (2.25 g four times daily) (p<0.05).

Some patients in Groups C and D exhibited a slight decline in renal function that did not meet the KDIGO criteria; these patients required hydration or dose reduction in order to continue TAZ/PIPC treatment (Table 2). In Groups A and C, the renal function of 94.4% and 68.8% of patients recovered without changing the TAZ/PIPC prescription, respectively. In Groups B and D, those with very severe or intractable pneumonia, significantly more patients in Group B (100%) completed the course of TAZ/PIPC as originally prescribed and without adjustment than in Group D (38.5%, p<0.05). And, patients which antibiotics were combined did not develop AKI.

The efficacy rates of TAZ/PIPC in Groups A and B were high (88.9% and 90.0%, respectively; Table 3). Efficacy was lowest (30.8%) in Group D, which had the highest incidence of AKI according to the KDIGO criteria, and was significantly lower than Group B (p<0.05).

The changes in mean SCr, eGFR-IND and CCr before and after TAZ/PIPC treatment are shown in Figs. 1, 2 and 3; these changes were both statistically significant in Group A (p<0.05, <0.05 and <0.05, respectively). The mean duration of treatment in Group A, with the lowest daily dose, was the longest, whereas the duration of treatment in Group D, with the highest daily dose, was the shortest. And the treatment periods of patients who were occurred AKI were almost administered within 7 d (Fig. 4).

**DISCUSSION**

As TAZ and PIPC undergo predominantly renal excretion, dosing schedules should be adjusted for patients with impaired renal function to prevent ad-
verse reactions.15) The urinary excretion rates of a single 4.5 g intravenous dose of TAZ and PIPC in healthy Japanese adults are reportedly 71.2% and 52.9%, respectively.16) When renal function is impaired, these high urinary excretion rates translate into an extension of the drug’s half-life. Generally, a penicillin-based antibiotic is considered to inhibit bacterial growth when its %TAM is ≥30%, and to show bactericidal effects when its %TAM is ≥50%.17) Shibata estimated the MIC of PIPC with a %TAM >30% or >50% to be 32 μg/mL and 16 μg/mL respectively, when administered to adults with normal renal function at a dose of 4.5 g three times daily.8)

We were unable to identify significant differences in SOFA disease severity scores between Groups A and B, or Groups C and D, but the judgement referring to

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Table 1. Patients’ Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18</td>
<td>10</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Male : Female</td>
<td>11 : 7</td>
<td>6 : 4</td>
<td>7 : 9</td>
<td>9 : 4</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>81.4±9.3</td>
<td>81.6±11.5</td>
<td>81.4±9.5</td>
<td>78.6±9.0</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.9±3.5</td>
<td>20.4±2.5</td>
<td>18.5±3.4</td>
<td>21.5±9.2</td>
<td>NS</td>
</tr>
<tr>
<td>Blood urine nitrogen (mg/dL)</td>
<td>42.9±22.4</td>
<td>31.1±7.8</td>
<td>36.2±23.6</td>
<td>34.1±13.5</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Cr concentration (mg/dL)</td>
<td>1.9±0.7</td>
<td>1.6±0.8</td>
<td>1.4±0.5</td>
<td>1.5±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>eGFR-NOR (mL/min/1.73 m²)</td>
<td>27.8±9.2</td>
<td>34.8±10.8</td>
<td>33.9±9.1</td>
<td>32.1±9.4</td>
<td>NS</td>
</tr>
<tr>
<td>eGFR-IND (mL/min)</td>
<td>23.3±6.7</td>
<td>28.8±7.8</td>
<td>29.7±7.4</td>
<td>27.8±6.9</td>
<td>A vs. C, p&lt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>12.1±8.7</td>
<td>12.0±9.4</td>
<td>11.7±7.6</td>
<td>12.2±9.8</td>
<td>NS</td>
</tr>
<tr>
<td>Serum alb concentration (g/dL)</td>
<td>3.0±0.6</td>
<td>2.8±0.7</td>
<td>2.7±0.7</td>
<td>2.9±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>32.9±17.5</td>
<td>31.2±16.1</td>
<td>28.1±14.5</td>
<td>30.2±15.5</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>25.4±19.2</td>
<td>19.0±8.1</td>
<td>22.2±14.1</td>
<td>31.6±25.2</td>
<td>NS</td>
</tr>
<tr>
<td>WBC (×10⁹/μL)</td>
<td>122.9±57.9</td>
<td>124.3±41.9</td>
<td>149.3±63.3</td>
<td>113.6±39.9</td>
<td>NS</td>
</tr>
<tr>
<td>PLT (×10⁹/μL)</td>
<td>22.6±6.0</td>
<td>20.2±10.2</td>
<td>21.2±9.8</td>
<td>26.3±5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Na concentration (mEq/L)</td>
<td>138.8±6.5</td>
<td>136.7±5.1</td>
<td>137.9±5.6</td>
<td>140.2±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>SOFA score</td>
<td>4.1±2.2</td>
<td>5.1±2.5</td>
<td>5.5±1.9</td>
<td>4.2±2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serious case of pneumonia (number of patients)</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>13</td>
<td>A vs. B, C vs. D, A vs. D p&lt;0.05</td>
</tr>
<tr>
<td>Concomitant antibiotics (number of patients)</td>
<td>VCM (1)</td>
<td>nothing</td>
<td>LVFX + nothing</td>
<td>ACV (1)</td>
<td>CLDM (1)</td>
</tr>
</tbody>
</table>

Data are presented as the mean±S.D. Comparisons of SOFA score and serious case of pneumonia were made in the four groups. Other comparisons were made between Group A and C, B and D. Abbreviations: NS, no significant differences between the four groups; Cr, creatinine; eGFR-NOR, estimated glomerular filtration rate normalized for body surface area; eGFR-IND, estimated glomerular filtration rate individualized for body surface area; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell count; PLT, platelet count; SOFA, Sequential Organ Failure Assessment; VCM, vancomycin; ACV, aciclovir; LVFX, levofloxacin; CLDM, clindamycin.

Table 2. Frequency of Acute Kidney Injury (Kidney Disease: Improving Global Outcomes definition), Decline in Renal Function and Recovery without Prescription Change

<table>
<thead>
<tr>
<th></th>
<th>2.25 g at a time</th>
<th>4.5 g at a time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n=18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group C (n=16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group D (n=13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuance without change of prescription</td>
<td>17</td>
<td>10*</td>
</tr>
<tr>
<td>Continuance with hydration or dose reduction because of a decline in renal function, but disagreeable with the KDIGO’s definition of acute kidney injury</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Continuance with hydration or dose reduction because of a decline in renal function, but disagreeable with the KDIGO’s definition of acute kidney injury</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Continuance with hydration or dose reduction because of a decline in renal function, but disagreeable with the KDIGO’s definition of acute kidney injury</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cases of acute kidney injury agreeable with the KDIGO’s definition (1)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Continuance with hydration or dose reduction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Continuance with hydration or dose reduction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Continuance with hydration or dose reduction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuance or change of prescription medicine</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuance or change of prescription medicine</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Discontinuance or change of prescription medicine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Frequencies of acute kidney injury agreeable with the KDIGO’s definition (%)</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Frequencies of acute kidney injury agreeable with the KDIGO’s definition (%)</td>
<td>25.0</td>
<td>38.5**</td>
</tr>
</tbody>
</table>

The frequency of acute kidney injury according to the Kidney Disease: Improving Global Outcomes (KDIGO) was highest in Group D. Comparisons were made between Group A and C, B and D. *p<0.05: comparison of the ratio of (1) to the total of (2) and (3) versus Group D. **p<0.05: versus Group B.
Table 3. Efficacy Rate of Each Groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=18)</th>
<th>Group B (n=10)</th>
<th>Group C (n=16)</th>
<th>Group D (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Continuance without change of prescription</td>
<td>16</td>
<td>9</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>2. Continuance with hydration or dose reduction because of a decline in renal function, but disagreeable with the KDIGO’s definition of acute kidney injury</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>3. Cases of acute kidney injury agreeable with the KDIGO’s definition</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

|                                | Efficacy rate (%) (only ①) | 88.9 | 90.0⁎ | 68.8 | 30.8 |

Efficacy rate was high in Groups A and B, and lowest in Group D. Comparisons were made between Group A and C, B and D. *p<0.05: versus Group D.

**Fig. 1.** Serum Cr Level Changes before and after Treatment in Groups A to D

The treatment periods within the groups are presented as means ± S.D. In serum Cr level of Group A, there were significant difference. Between Group A and C, Group B and D, the treatment periods were no significantly different (Mann-Whitney U test). Abbreviation: creatinine, Cr. *p<0.05.

**Fig. 2.** eGFR-IND Changes before and after Treatment in Groups A to D

In eGFR individualized for body surface area (eGFR-IND) of Group A, there were significant difference. Abbreviations: estimated glomerular filtration rate, eGFR; individualized, IND. *p<0.05.
the report of Kohno et al. clarified the existence of serious cases in the Group B and D, significantly more than Group A and C. It was indicated that the regimens for Group B and D were suitable for the recommendation.

And the higher SOFA score of Group C compared with Group A suggests that physicians in our institution reduced the dosing frequency in those with severe pneumonia. As the eGFR-IND and CCr was significantly lower in Group A than Group C, it appears that the dose was also reduced in patients judged to be at highest risk of renal impairment.

It is challenging to establish whether AKI identified in our cohort was caused by the severity of pneumonia or the TAZ/PIPC used to treat it, particularly when dose and dosing frequency can be adjusted. Our observation that the incidence of AKI was significantly higher in Group D (4.5 g three times daily) than Group B (2.25 g four times daily) suggests that the higher dose is the most likely cause, and the absence of a difference between Group A (2.25 g three times daily) and Group C (4.5 g twice daily) suggests that higher doses may provoke AKI when the dosing frequency is increased. We cannot rule out, however, that disease severity may also have provoked the renal impairment observed in Group C.

Although SCr did not increase to more than 1.5-fold of the baseline value (measured 7 d before TAZ/PIPC treatment began) in every case, all cases in which there was an increase in SCr were in Groups C and D; in these cases, hydration or dose reduction was necessary to continue TAZ/PIPC administration. Conversely, most of the patients in Groups A and B, who received lower doses, were able to complete treatment without the need for any specific measures such as hydration or dose reduction. This suggests that lower doses achieve the desired goal of reducing the risk of renal impairment.

We also found that TAZ/PIPC was less efficacious in Group D than Group B. Even with a reduced dosing frequency, the higher dose appears to provoke AKI and likely leads to a further reduction in the dose. We judge that in cases in whom the TAZ/PIPC dose and frequency were unchanged, its efficacy was broadly comparable between the four groups.

We observed that, compared with baseline values, SCr fell significantly and the eGFR-IND and CCr rose significantly after treatment with TAZ/PIPC in Group A (who received the lowest daily dose). There were no significant changes in SCr, eGFR-IND and CCr in Group B, C and D. But in Group B (who received the lower dose) eGFR-IND and CCr tended to rise. Treatment duration was longest in Group A.
and shortest in Group D. When AKI occurred, TAZ/PIPC was discontinued, while it was continued if there was no adverse reaction or complications. Five patients (38.5%) suffered AKI in Group D, and the treatment period was curtailed in all cases.

The mechanism by which TAZ/PIPC affects renal function is mainly attributed to the participation of PIPC in the organic anion transporters (OATs). The β-lactamase antibiotics, including PIPC, are excreted into the urine via the OATs located on the basolateral membranes of the proximal renal tubules. Furthermore, PIPC inhibits OATs. Landersdorfer et al. has found that when 3.0 g of PIPC was administered alone, PIPC clearance was smaller than when 1.5 g of PIPC was administered.

Regarding the elimination of PIPC, Aronoff et al. identified non-linear drug clearance in patients with normal renal function; in patients with severe renal failure, renal clearance of PIPC occurred very slowly. This explains the saturation of PIPC in the renal tubules, and its prolonged elimination after a higher dose. Based on the existing evidence and our results, it seems likely that the deterioration in renal function in patients with pre-existing renal disorders with infection requiring treatment with a high dose of TAZ/PIPC can be explained by the effect of PIPC on OATs in the renal tubules.

The treatment period was investigated. AKI was found to occur mostly within one week after administration. Therefore, it is necessary to carefully observe renal function during one week of administration.

And, it is thought that it is unclear if this study is also considered for other disease unless study is done. However, for example, about urinary tract infection, Shiba also reported dosing regimens for patients with impaired renal function. When administered to patients with renal function equivalent to this study, it is administered at a dose of 2.25 g twice daily, even in severe urinary tract infection, 4.5 g twice daily or 2.25 g three times daily. For the reason for the small dose as described above, it is considered that the pharmacological distribution of TAZ/PIPC to renal is better than that of the lung. The dosing regimens in case of severe urinary tract infection is same as Group A and Group C. Therefore, for severe urinary tract infection, when it is administered at a dose 4.5 g twice daily, it is needed to be careful because AKI are likely to occur.

Our study had some limitations. It was a single-center study with a relatively small sample size, especially in Group B (2.25 g four times daily). As it was an observational study, and not randomized or controlled, it may have been subject to unmeasured confounding factors that could have introduced bias. Despite these limitations, our results suggest that the higher dose was the cause of worsening renal function. A TAZ/PIPC dosing regimen of 4.5 g twice or three times daily, or 2.25 g three or four times a daily, has been recommended for patients with an eGFR-IND between 10 and 40 mL/min. Our finding that higher doses were associated with lower efficacy and a greater risk of AKI, suggest that reducing the dose rather than the frequency of administration is most likely to preserve renal function while treating an underlying pneumonia in high risk patients.

Conflicts of Interest None of the authors has a conflict of interest to declare.

REFERENCES


