Effect of piperacillin/tazobactam restriction on usage and rates of acute renal failure

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A piperacillin/tazobactam (PT) restriction was initiated at our institution on 15 July 2012 requiring clinical pharmacy or infectious diseases approval for durations exceeding 72 h. A retrospective review was undertaken to determine whether this restriction decreased PT usage and/or rates of acute renal failure (ARF) (defined as a 50 % increase or 0.5 mg dl$^{-1}$ increase in serum creatinine from baseline). Patients prescribed at least 1 day of PT with a creatinine clearance of $\geq$39 ml min$^{-1}$ at the time of initiation in the 3 months prior to the restriction were compared with patients in the 5 months after restriction implementation. Overall, 115 unique patients were included in the pre-implementation group and compared with 117 unique patients in the post-implementation group. The pre-implementation group received a mean of 5.22 days of PT, compared with 4.71 days in the post-implementation group ($P=0.224$). Ten per cent (12/115) of patients in the pre-implementation group developed ARF compared with 9.17 % (11/120) of patients in the post-implementation group ($P=0.0309$). Ninety-five patients in the pre-implementation group and 91 in the post-implementation group received combination therapy with vancomycin. ARF occurred in 11.6 % (11/95) of those in the pre-implementation group and 12.1 % (11/91) in the post-implementation ( $P>0.05$). Overall, 11.8 % (22/186) of patients who received therapy with PT and vancomycin developed ARF, compared with 1.7 % (1/56) who received PT monotherapy ($P<0.0001$). This restriction resulted in a numeric reduction in the number of PT days in the post-implementation group and a significant reduction in the rate of ARF.

INTRODUCTION

Piperacillin/tazobactam (PT) is a broad-spectrum antibiotic that provides coverage against many Gram-positive, Gram-negative (including Pseudomonas aeruginosa) and anaerobic organisms, and has been approved by the US Food and Drug Administration (FDA) to treat community-acquired and nosocomial pneumonias, uncomplicated skin and skin structure infections (including diabetic foot infections), and intra-abdominal infections (as recommended by the manufacturer, Pfizer, 2012). Because of the broad spectrum of activity it provides, along with FDA approval to treat diabetic foot infections and nosocomial pneumonias, PT has been used extensively within our facility.

The current Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines on antimicrobial stewardship recommend the implementation of antibiotic restriction to reduce unnecessary use of antimicrobial agents, as well as a reduction in overall hospital costs. These guidelines consider antibiotic restriction and pre-authorization as the most effective methods in controlling the use of antimicrobial agents (Dellit et al., 2007). In agreement with the IDSA and SHEA antimicrobial stewardship guidelines, Dunn et al. (2011) demonstrated that a pharmacist-driven antimicrobial stewardship programme significantly decreased the number of days of intravenous antimicrobial therapy and the number of days until intravenous antimicrobial therapy was transitioned to oral therapy.

At the VA St Louis Health Care System, PT was previously classified as an unrestricted antibiotic, which allowed any provider to prescribe the antibiotic with an indefinite duration. A previous study completed at the VA St Louis Health Care System revealed high rates of PT prescribing with increasing cases of acute renal failure (ARF) (defined as a 50 % increase or 0.5 mg dl$^{-1}$ increase in serum creatinine from baseline) (Moenster et al., 2014). Based on these data, the decision was made on 15 July 2012 to place PT on 72 h restriction,
meaning that any inpatient provider could order the antibiotic, but each order would be given a 72 h stop date. After the 72 h have expired, the order is subject to review by an infectious diseases physician or a clinical pharmacy specialist. The reviewer searches the electronic medical record for culture data, signs or reported symptoms of ongoing infection and other patient-specific factors to determine whether continued therapy is warranted, whether there is no further need for antibacterial therapy or whether a narrower-spectrum agent could be used. These recommendations are communicated to the primary teams in the form of Antibiotic Expiration notes written in the electronic medical record.

In this evaluation, we reviewed what, if any, clinical impact this restriction had on PT usage, and made an effort to better describe the rates of ARF in patients prescribed PT alone or PT with vancomycin.

METHODS

We conducted a retrospective cohort study of patients at the VA St Louis Health Care System – John Cochran Division prescribed more than 1 day of PT therapy with a creatinine clearance (CrCl) of $\geq 39 \text{ ml min}^{-1}$. Patients were analysed from 15 April 2012 to 31 December 2012. Patients were divided into two groups: pre- and post-implementation of the PT restriction. The pre-implementation group encompassed patients 2.5 months prior to implementation of the PT restriction (15 April–30 June 2012) and the post-implementation group encompassed patients 5 months after restriction was implemented (1 August–31 December 2012). All procedures were in accordance with the ethical standards of the VA St Louis Health Care System on human experimentation.

The primary outcome was mean days of PT therapy per course in the pre-implementation group compared with the post-implementation group. Because of institutional data suggesting that the combination of vancomycin and PT may be more nephrotoxic than either agent alone, the mean number of days of PT and vancomycin combination therapy between groups was also compared. We also compared rates of ARF between groups.

To evaluate the potential of confounders between groups that may affect rates of ARF, nephrotoxic medications were assessed between groups [loop diuretics, angiotensin-converting enzyme inhibitors (ACEIs), aminoglycosides and radiocontrast dye administration]. Other variables that were evaluated included age at initiation, PT indication, concomitant antibiotics, serum creatinine at initiation, CrCl at initiation (using the Cockcroft–Gault equation), peak serum creatinine during PT therapy and lowest CrCl during therapy. Clinical pharmacy notes entered in the patient’s medical chart assessing the appropriateness of PT therapy, as well as dosing, were also compared between the pre- and post-implementation groups.

As this was an evaluation of an antimicrobial stewardship process change, no power calculation was completed; all patients in the given time frame receiving at least 1 day of PT and with a CrCl of $\geq 39 \text{ ml min}^{-1}$ were included. Rates of ARF were assessed between groups using a $\chi^2$ test with a predetermined expected event rate of 15 % in each group. All other comparisons were performed using Student’s $t$-test. Comparisons were determined to be statistically significant with a $P$-value of $<0.05$.

RESULTS

Overall, 232 unique patients were included in the study encompassing a total of 242 courses of PT therapy. One hundred and fifteen unique patients were included in the pre-implementation group treated with 120 courses of PT therapy, compared with 117 unique patients in the post-implementation group treated with 122 courses of PT therapy. Baseline characteristics were comparable between the groups and are shown in Table 1. All patients included in this analysis were male.

The three most common indications for PT therapy in the pre-implementation group were cellulitis ($n=32$), pneumonia ($n=24$) and diabetic foot infections ($n=12$), which were comparable to the indications in the post-implementation group: pneumonia ($n=30$), cellulitis ($n=25$) and diabetic foot infections ($n=11$). Concomitant loop diuretics ($n=17$ vs 19), ACEIs ($n=37$ vs 39) and aminoglycosides (0 vs 1) were compared at initiation of PT therapy, and radiocontrast dye administration ($n=43$ vs 49) was assessed during PT therapy between the pre- and post-implementation groups, and no significant differences between groups were found.

When assessing PT usage between groups, the post-implementation group received on average 4.71 days of PT therapy per course compared with the pre-implementation group at 5.22 days of PT therapy per course ($P=0.224$). The mean number of vancomycin and PT combination therapy days per course was also lower in the post-implementation group at 3.27 days compared with the pre-implementation group at 4.00 days, but was not significant ($P=0.105$). Fig. 1 represents the ranges of duration of therapy in the pre- and post-implementation groups.

In total, there were 23 episodes of ARF with an overall incidence of 9.5 %. ARF was statistically more common in the pre-implementation group compared with the post-implementation group [10.0 % ($n=12$) vs 9.0 %]

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre-implementation ($n=120$)</th>
<th>Post-implementation ($n=122$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>64.8</td>
<td>63.5</td>
<td>0.354</td>
</tr>
<tr>
<td>Mean duration of PT therapy (days)</td>
<td>5.22</td>
<td>4.71</td>
<td>0.224</td>
</tr>
<tr>
<td>Mean duration of combination therapy (days)</td>
<td>4.00</td>
<td>3.27</td>
<td>0.105</td>
</tr>
<tr>
<td>Episodes of ARF ($n$)</td>
<td>12</td>
<td>11</td>
<td>0.039</td>
</tr>
<tr>
<td>Serum creatinine at initiation (mg dl$^{-1}$)</td>
<td>1.05</td>
<td>0.99</td>
<td>0.116</td>
</tr>
</tbody>
</table>
Most interestingly, of the 23 episodes of ARF, 22 occurred in patients receiving vancomycin and PT combination therapy, while one episode occurred in the PT monotherapy group. In total, there were 186 courses of therapy in the PT and vancomycin combination therapy group with an 11.8% rate of ARF, compared with 56 courses of therapy in the PT monotherapy group with a 1.7% occurrence rate ($P<0.0001$).

Patients who developed ARF were comparable with regard to age, baseline serum creatinine and creatinine clearance at initiation in the pre- and post-implementation groups (Table 2). In patients who developed ARF concomitant nephrotoxic medications at initiation of PT therapy in the pre- and post-implementation groups including loop diuretics ($n=1$ vs 5, respectively), ACEIs ($n=3$ vs 1, respectively) and aminoglycosides (both 0) as well as radiocontrast dye administered during PT therapy ($n=4$ vs 3, respectively) were also not significantly different between the groups.

When comparing patients who experienced ARF with those who did not, patients with ARF received more mean days of PT therapy compared with those who did not develop ARF (6.34 vs 4.82 days; $P=0.036$) (Fig. 2). In addition, vancomycin and PT combination therapy days were also significantly higher in patients who developed ARF at a mean of 5.04 days compared with patients without ARF with a mean of 3.49 days ($P=0.021$).

Clinical pharmacist notes assessing PT therapy and offering recommendations for changing therapy, where appropriate, were more common in the post-implementation group compared with the pre-implementation group. Clinical pharmacist notes were written on 34 courses of PT therapy in the pre-implementation group (28.3%) compared with the post-implementation group, in which clinical pharmacist notes were written on 78 courses of PT therapy (63.9%).

**DISCUSSION**

A 72 h PT restriction initiated at the VA St Louis Health Care System resulted in a reduction in ARF in the post-implementation group when compared with the pre-implementation

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**Table 2. Comparison between ARF and no-ARF groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ARF ($n=23$)</th>
<th>No ARF ($n=219$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>60.9</td>
<td>64.5</td>
<td>0.053</td>
</tr>
<tr>
<td>Mean duration of PT therapy (days)</td>
<td>6.34</td>
<td>4.82</td>
<td>0.036</td>
</tr>
<tr>
<td>Mean duration of combination therapy (days)</td>
<td>5.04</td>
<td>3.49</td>
<td>0.021</td>
</tr>
<tr>
<td>Serum creatinine at initiation (mg dl$^{-1}$)</td>
<td>1.05</td>
<td>1.02</td>
<td>0.638</td>
</tr>
<tr>
<td>Monotherapy ($n$)</td>
<td>1</td>
<td>55</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Total days of PT therapy in the pre- and post-implementation groups. 95% of PT courses are represented in bar graph with minimum and maximum extreme durations represented on line portion within respective groups.

**Fig. 2.** Mean number of antibiotic therapy days. Filled columns, ARF; shaded columns, no ARF.
group, although this difference amounted to only a single case. The 72 h PT restriction resulted in a numerical decrease in the mean number of days per PT course, but this difference did not achieve statistical significance. It is worth mentioning, however, that 115 unique PT patients were identified in 2.5 months in the pre-implementation period, but it took 5 months in the post-implementation period to identify a similar number of cases, signalling that the restriction could have played a role in slowing the rate of PT prescribing. More than twice as many clinical pharmacist notes were written on courses of PT therapy in the post-implementation group (63.9 %) when compared with the pre-implementation group (28.3 %). More frequent assessment of PT therapy in the post-implementation group by clinical pharmacists could have resulted in more appropriate, patient-specific dosing of PT therapy and earlier de-escalation to less nephrotoxic antibiotics.

The increase in clinical pharmacy review of PT therapy in the post-implementation group is in accordance with the findings of a study completed by Yam et al. (2012), who demonstrated that a pharmacy-directed antimicrobial stewardship programme increased pharmacist-initiated interventions from a mean of 2.1 per week to a mean of 6.8 per week after implementation of their programme. These authors also demonstrated a decrease in overall hospital costs, as well as a decrease in the occurrence of Clostridium difficile infections.

Patients who ultimately developed ARF received significantly longer courses of PT therapy, as well as more days of vancomycin and PT combination therapy, compared with patients who did not experience ARF. Of the 23 episodes of ARF, the majority occurred in patients receiving vancomycin and PT combination therapy compared with PT monotherapy (22 cases vs one case). The sole patient in the PT monotherapy group who developed ARF also received radiocontrast dye during hospitalization.

Further studies should be conducted on vancomycin and PT combination therapy with larger patient populations to assess the true incidence rate with this antibiotic combination, especially when compared with other therapeutic options. However, patients receiving combination therapy with vancomycin and PT should be closely monitored for the development of ARF and adjusted to a less nephrotoxic regimen when possible and, if appropriate, based on the findings in our study.

Since the completion of the present evaluation, several studies have been published assessing the risk of ARF with PT and vancomycin combination therapy. Burgess & Drew (2014) assessed vancomycin-induced nephrotoxicity with and without concomitant PT therapy, finding a statistically increased risk with vancomycin and PT combination therapy (16.3 %) compared with vancomycin monotherapy (8.1 %) ($P=0.041$). Gomes et al. (2014) conducted a single-centre, retrospective, matched-cohort study of patients receiving PT and vancomycin or PT and cefepime, and found a significantly higher rate of ARF in the PT and vancomycin group (34.8 vs 12.5 %; $P<0.0001$). Similarly, Moenster et al. (2014) compared the rates of ARF in osteomyelitis patients receiving PT and vancomycin therapy with cefepime and vancomycin therapy, finding a non-significant increase in cases of ARF with PT and vancomycin (29.3 %) compared with cefepime and vancomycin (13.3 %) ($P=0.099$). Most recently, Davies et al. (2015) retrospectively evaluated patients from 2005 to 2009 at a single centre who were prescribed vancomycin monotherapy, vancomycin and PT, or vancomycin with an alternative Gram-negative agent. These authors did not find a significant risk of ARF associated with vancomycin and PT (risk ratio $=1.1$, 95 % confidence interval 0.99–1.2) or vancomycin and an alternate agent (risk ratio $=1.1$, 95 % confidence interval 0.98–1.2) when compared with vancomycin alone.

The present study has several limitations that must be discussed in combination with the results. The time frames for inclusion could have encompassed a larger date range with the same number of months included in the pre-implementation and post-implementation groups to account for seasonal variations in antibiotic-prescribing patterns. In addition, the usage of other broad-spectrum antibiotics could have been analysed to determine whether a numerical decrease in PT usage in the post-implementation group led to increased prescribing of other broad-spectrum antibiotics. Another limitation of this evaluation was the failure to assess comorbidities or other factors that may have had an effect on the patients’ renal function; however, all patients included did have a baseline CrCl of $\geq 39 \text{ ml min}^{-1}$.

**CONCLUSIONS**

The implementation of a 72 h PT restriction at our institution led to a significant decrease in the rate of ARF and a numerical decrease in the mean days of PT therapy; additionally, it may have slowed the rate of PT prescribing. The 72 h PT restriction also led to a notable increase in pharmacist reviews of PT courses. In addition, combination therapy with vancomycin and PT significantly increased the risk of ARF compared with PT monotherapy.

**REFERENCES**


