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Short Communication

Impact of piperacillin/tazobactam on nephrotoxicity in patients with Gram-negative bacteraemia

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ABSTRACT

Piperacillin/tazobactam (TZP) has been associated with nephrotoxicity in patients receiving vancomycin. Its impact on nephrotoxicity in patients with Gram-negative bacteraemia (GNB) is unclear. This study evaluated the impact of TZP on nephrotoxicity in patients with GNB. This retrospective cohort included patients aged ≥18 years receiving ≥48 h of therapy for bacteraemia due to *Escherichia coli, Pseudomonas aeruginosa, Enterobacter, Klebsiella, Acinetobacter* or *Stenotrophomonas maltophilia* from 1/01/2008–8/31/2011. Patients with baseline serum creatinine (SCr) ≥3.5 mg/dL, polymicrobial infection or recurrent bacteraemia were excluded. Nephrotoxicity was defined as a ≥0.5 mg/dL increase in SCr or ≥50% increase from baseline for ≥2 consecutive days. Any variable demonstrating a 10% change in exposure effect was retained in the final model. All variables biologically reasonable causes of nephrotoxicity were also considered for inclusion. The median age of the cohort ($n = 292$) was 76 years; 38.0% had a cancer diagnosis and ICU residence was common (21.9%). There was no difference in nephrotoxicity incidence based on days of TZP received (0 days, 13.6%; 1–2 days, 14.7%; 3–4 days, 6.9%; ≥5 days, 16.7%; $P = 0.71$). In multivariable analysis, baseline SCr, total body weight and vasopressor use were independently associated with nephrotoxicity. Duration of TZP was not associated with nephrotoxicity in multivariable analysis (1–2 days, OR = 0.91, 95% CI 0.39–2.12; 3–4 days, OR = 0.48, 95% CI 0.10–2.46; ≥5 days, OR = 0.57, 95% CI 0.11–3.02). In this cohort of GNB patients, duration of TZP was not associated with nephrotoxicity.

1. Introduction

Patients with Gram-negative bacteraemia (GNB) can be treated with various antimicrobial agents, including β-lactams and fluoroquinolones. Piperacillin/tazobactam (TZP) is one of the most common choices for these patients owing to its inclusion in multiple clinical practice guidelines [1,2]. Its use has also been encouraged given that cephalosporins and fluoroquinolones have been more frequently associated with the emergence of multidrug-resistant pathogens [3]. In addition, TZP has been regarded as a 'safe' antimicrobial given that its adverse effect profile is largely devoid of frequent or severe adverse events, other than those expected with penicillin derivatives [4]. Therefore, TZP was believed to be a drug that was not associated with nephrotoxicity.

However, other investigators have noted an increased risk of nephrotoxicity when TZP is combined with vancomycin [5,6]. Studies evaluating TZP therapy regardless of vancomycin use have suffered from using non-standard or ill-defined measures of nephrotoxicity [7,8]. These studies and others have not evaluated the effect of TZP therapy on the incidence of nephrotoxicity specifically in patients with GNB [9,10].

Therefore, a retrospective cohort study evaluating the impact of TZP compared with other antimicrobial regimens in patients with GNB was conducted.

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2. Methods

2.1. Overview of study design

The methods for this retrospective cohort study have been described previously [11]. Briefly, the retrospective cohort included patients admitted to an 888-bed community teaching hospital with GNB from 1 January 2008 to 31 August 2011. The study protocol was reviewed and approved by the Institutional Review Board with a Waiver of Informed Consent and Health Insurance Portability and Accountability Act approved due to the retrospective nature of the research. All patients aged ≥18 years admitted with bacteraemia due to *Escherichia coli, Pseudomonas aeruginosa, Enterobacter* spp., *Klebsiella* spp., *Acinetobacter* spp. or *Stenotrophomonas maltophilia* during their hospital stay were screened for eligibility. Patients were excluded if they did not have a height and weight recorded in the chart, had a polymicrobial infection, had a baseline serum creatinine (SCr) of ≥3.5 mg/dL or had a previous episode of GNB. Patients who met the inclusion/exclusion criteria had their charts reviewed for demographics, medical history and source of bacteraemia.

2.2. Variable definitions

The primary outcome was the incidence of nephrotoxicity in patients receiving TZP versus other antimicrobial regimens for GNB. Patients were grouped by the number of days they received TZP for GNB (0, 1–2, 3–4 or ≥5 days). The 0 days group did not receive any doses of TZP. Adequate empirical antibiotic therapy was defined as receipt of at least one antimicrobial agent to which the causative micro-organism was susceptible within 24 h of blood culture collection. Nephrotoxicity was defined as an increase of 0.5 mg/dL or a ≥50% increase in SCr from baseline for at least two consecutive days [12]. Baseline SCr used was the value closest to the time of blood culture extraction. Pitt bacteraemia scores were computed at the time of blood culture extraction [13].

2.3. Statistical analyses

Nominal data were analysed using a Fisher's exact test or χ^2 test as appropriate. Continuous data were assumed to be non-normally distributed and were evaluated using a Kruskal–Wallis test. A stratified analysis on potential confounders was performed, and the Cochran–Mantel–Haenszel χ^2 statistic was evaluated. Any variable demonstrating a 10% change in the odds ratio was retained in the final model [14]. All variables conceptually regarded as biologically reasonable causes of nephrotoxicity were also considered for inclusion in the multivariable model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable in the multivariable model with robust standard errors. A stratified multivariable analysis was also conducted using an age cut point of 75 years. A cohort of 350 patients would allow us to evaluate the association of five variables with the risk of nephrotoxicity, assuming that 15% of patients developed nephrotoxicity [15].

Statistical significance was defined as a two-tailed *P*-value of <0.05. All analyses were performed using Stata Statistical Software: Release 15 (StataCorp LLC, College Station, TX).

3. Results

Of the 292 patients included in the study, 13% developed nephrotoxicity. There was no difference between rates of nephrotoxicity based on the number of days of TZP received (0 days, 13.6%; 1–2 days, 14.7%; 3–4 days, 6.9%; ≥5 days, 16.7%; $P = 0.71$). The empirical antibiotics received by the 0 days group included aminoglycosides ($n = 7$), carbapenems ($n = 35$), cephalosporins ($n = 70$), fluoroquinolones ($n = 47$), monobactams ($n = 7$) and/or other ($n = 10$). The median duration of TZP was 2 days for patients who received this antibiotic. The cohort was primarily comprised of patients who were aged >65 years (73%), with a median patient age of 76 years. A cancer diagnosis was present in 38.0% of patients and 21.9% of patients were intensive care unit (ICU) residents. The number of days of TZP given was associated with the length of hospital stay prior to bacteraemia ($P < 0.001$). The median lengths for hospital stay prior to bacteraemia were 4 days (0 days of TZP), 4 days (1–2 days of TZP), 5 days (3–4 days of TZP) and 10.5 days (≥5 days of TZP). There were more patients with chronic kidney disease (38.9%; $P = 0.05$) in the ≥5 days of TZP group. No other statistically significant differences were noted between the other baseline characteristics (Table 1). The most common source of infection was the urinary tract (66%), followed by intra-abdominal (23%), intravenous catheter (4%), other (4%) and undocumented (3%).

Five factors were found to be associated with nephrotoxicity in the univariable analysis (Table 2). Factors associated with nephrotoxicity included baseline SCr, ICU length of stay, Pitt bacteraemia score (1 point increments), total body weight (1 kg increments) and vasopressor use. Duration of TZP therapy was not associated with nephrotoxicity in the univariable analysis.

Similarly, the duration of TZP use was not associated with nephrotoxicity in the multivariable analysis (Table 3). Baseline SCr (OR = 1.86, 95% CI 1.11–3.09), total body weight (OR = 1.02, 95% CI 1.00–1.03) and vasopressor use (OR = 6.97, 95% CI 3.17–15.32) were factors independently associated with nephrotoxicity.

4. Discussion

This study was designed to evaluate the impact of TZP therapy on the incidence of nephrotoxicity compared with other antimicrobial regimens in patients with GNB. It was found that TZP was not associated with nephrotoxicity in these patients.

Phase 1–3 studies of TZP observed a low, but non-zero, risk of nephrotoxicity with its use [4]. More recent studies focusing on the combination of vancomycin and TZP have reported significantly higher rates of acute renal failure than comparator groups [6,16]. A retrospective study evaluating biapenem versus TZP in elderly patients with nursing- and healthcare-associated pneumonia reported a higher rate of nephrotoxicity for TZP (6/53 vs. 0/53; $P = 0.005$) [7]. Another study found that TZP was associated with delayed renal recovery in critically ill patients; the same study indicated more patients having an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 while on TZP versus other antibiotics both at entry and last day of follow-up [8].

Previous studies have been inconsistent regarding the impact of TZP on nephrotoxicity. Some studies have suggested that TZP does negatively impact renal function. However, some of these studies findings for this association did not consider concomitant vancomycin use and/or did not use a standard definition of nephrotoxicity [6,7]. Karino et al. observed a much lower rate of nephrotoxicity compared with the results in the current study or the results found by others using a standard definition [5–7,16]. A recent study by Schreier et al. found that 24–72 h of concomitant vancomycin and TZP was not associated with nephrotoxicity or 60-day adverse renal outcomes [17]. The clinical impact of delayed return to normal function used by Jensen et al. is unknown [8].

The current findings were also consistent in that TZP was not associated with nephrotoxicity [9,10]. Balcı et al. found a similar incidence of nephrotoxicity for vancomycin monotherapy (16%), TZP monotherapy (16%) and vancomycin/meropenem combination therapy (10%) [9]. Rutter and Burgess found similar rates of nephrotoxicity for ampicillin/sulbactam and TZP (9% vs. 11%; $P = 0.14$) [10]. The results of the current study differ from Rutter and Burgess

Table 1
Baseline characteristics of the cohort by days of piperacillin/tazobactam (TZP) therapy[a].

Characteristic	Entire cohort ($n=292$)	0 days ($n=170$)	1–2 days ($n=75$)	3–4 days ($n=29$)	≥5 days ($n=18$)	*P*-value
Male sex (%)	37.3	34.7	34.7	44.8	61.1	0.13
Age (years)	76 (63.5–85)	75.5 (61–86)	76 (66–85)	78 (59–84)	80 (643–85)	0.98
Weight (kg)	73.2 (60.8–89.0)	72.34 (60.23–87.3)	72.1 (60.8–86.7)	80.2 (63–97.7)	81.8 (74.7–92.5)	0.09
Height (inches)	65.5 (63–69)	65 (63–69)	65 (63–68)	66 (62–69)	68 (65–70)	0.12
Cirrhosis (%)	8.6	9.4	9.3	3.5	5.6	0.84
Chronic kidney disease (%)	17.1	15.9	18.7	6.9	38.9	0.05
Cancer (%)	38.0	38.8	34.7	41.4	38.9	0.91
COPD (%)	15.8	14.7	16.0	24.1	11.1	0.59
Diabetes (%)	28.4	30.0	24.0	20.7	44.4	0.26
Baseline SCr (mg/dL)	1.3 (0.9–1.9)	1.3 (0.9–1.7)	1.4 (0.9–2.0)	1.2 (0.9–1.5)	1.5 (1.0–2.4)	0.41
Length of stay prior to bacteraemia (days)	5 (3–8.5)	4 (3–8)	4 (3–8)	5 (3–11)	10.5 (7–15)	<0.001
ICU residence (%)	21.9	22.4	22.7	17.2	22.2	0.94
Vasopressor use (%)	17.1	16.5	18.7	10.3	27.8	0.47
Pitt bacteraemia score	1 (1–3)	1 (1–3)	2 (1–3)	1 (1–2)	2 (1–4)	0.70
Adequate empirical antimicrobials (%)	92.8	94.1	92.0	93.1	83.3	0.36

COPD, chronic obstructive pulmonary disease; SCr, serum creatinine; ICU, intensive care unit.
[a] Values are the median (interquartile range) unless otherwise stated.

Table 2
Univariable analysis of nephrotoxicity.

Variable	OR	95% CI
Adequate empirical antimicrobial coverage	0.46	0.16–1.35
Baseline SCr (1 mg/dL increments)	1.88	1.20–2.95
Cancer	1.66	0.84–3.28
Chronic kidney disease	1.83	0.83–4.07
Cirrhosis	1.71	0.60–4.88
Diabetes	1.14	0.55–2.37
Days of TZP therapy		
0	Ref.	N/A
1–2	1.10	0.50–2.39
3–4	0.47	0.11–2.13
≥5	1.28	0.34–4.77
ICU length of stay (1 day increments)	1.18	1.07–1.30
Male sex	1.35	0.69–2.66
Patient age (1 year increments)	1.00	0.99–1.02
Pitt bacteraemia score (1 point increments)	1.22	1.08–1.36
TBW (1 kg increments)	1.01	1.00–1.03
Vasopressor use	6.80	3.27–14.16

OR, odds ratio; CI, confidence interval; SCr, serum creatinine; TZP, piperacillin/tazobactam; N/A, not applicable; ICU, intensive care unit; TBW, total body weight.

in that no association between the duration of TZP therapy and nephrotoxicity was found.

The incidence of nephrotoxicity in this cohort is consistent with other previous investigations that use a standard definition of nephrotoxicity [9,10]. The nephrotoxicity rate for the current cohort (13%) is higher than the typical 0–5% reported in phase 3 clinical trials. This likely reflects that patients recruited in phase 3 clinical trials are not reflective of the patients that a drug receives regulatory approval for. There may be a higher baseline rate of nephrotoxicity in patients with bacteraemia owing in part to the severity of disease. This finding emphasises the impact of standard nephrotoxicity definitions on the incidence of nephrotoxicity reported. Clinical trials should use a standardised nephrotoxicity definition to help standardise the reporting of nephrotoxicity and to help clinicians make more informed decisions regarding the actual risk of nephrotoxicity.

This study has several limitations. Cohort studies, whether prospective or retrospective, are unable to exclude the possibility of unmeasured confounding. There would also be multiple issues with conducting a randomised clinical trial to answer this question. Conducting a randomised trial in the setting of bacteraemia is difficult given the small number of patients as well as challenges with randomising patients prior to initiation of antimicrobial therapy. Clinical trials also often suffer from a lack of external validity owing to the inclusion/exclusion criteria not being consistent with how the intervention is actually used in practice. We did include patients with chronic kidney disease since these patients are more likely to develop bacteraemia than patients who do not have kidney disease [18]. The use of a single centre may limit the external validity of the findings. A larger sample size may have been able to determine additional associations impacting the incidence of nephrotoxicity. The 292 eligible patients in this cohort are the number of patients with GNB in 3.7 years at an 888-bed institution. The stratified analysis by age should be evaluated with caution owing to the imprecision of these estimates. Information regarding receipt of vancomycin was not collected.

Since patients with polymicrobial infections were excluded, the likelihood of sustained concomitant vancomycin use is low. Also, the risk of nephrotoxicity should have been even higher in the

Table 3
Multivariable analysis of nephrotoxicity.

Variable	Entire cohort		Age <75 years		Age ≥75 years	
	OR	95% CI	OR	95% CI	OR	95% CI
Baseline SCr (1 mg/dL increments)	1.86	1.11–3.09	2.91	1.30–6.50	1.11	0.60–2.06
Days of TZP therapy						
0	Ref.	N/A	Ref.	N/A	Ref.	N/A
1–2	0.91	0.39–2.12	0.41	0.11–1.45	1.51	0.48–4.76
3–4	0.48	0.10–2.46	0.57	0.05–7.08	0.37	0.05–2.85
≥5	0.57	0.11–3.02	0.41	0.01–11.29	1.26	0.22–7.41
Vasopressor use	6.97	3.17–15.32	5.31	1.21–23.26	8.56	3.00–24.55
TBW (1 kg increments)	1.02	1.00–1.03	1.01	0.99–1.03	1.02	0.99–1.04

OR, odds ratio; CI, confidence interval; SCr, serum creatinine; TZP, piperacillin/tazobactam; N/A, not applicable; TBW, total body weight.

TZP group if a substantial number of patients received concomitant vancomycin. We did collect data on the use of select nephrotoxins (aminoglycosides, polymyxins, vasopressors) that have previously been associated with nephrotoxicity. We did not focus on other nephrotoxins [e.g. angiotensin-converting enzyme (ACE) inhibitors, cisplatin, loop diuretics] that may be of interest. We also did not document the infusion time of the TZP regimen. However, Cotner et al. have reported that the infusion duration of β-lactams is not associated with nephrotoxicity [19].

Other definitions of nephrotoxicity have been developed that would have provided more information regarding the severity of kidney injury experienced than the definition used in this study [20]. The Acute Kidney Injury Network (AKIN) classification would have possibly resulted in a higher incidence of nephrotoxicity given that the 0.3 mg/dL or 2 $\times$ increase in SCr definition is less than the 0.5 mg/dL or $\geq$50% increase used in the current study. The Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease (RIFLE) classification would likely result in a similar overall nephrotoxicity rate for patients with a low or normal SCr, while finding lower rates of nephrotoxicity for patients with an increased baseline SCr. Both measures can use urine output to evaluate the degree of kidney injury. We did not collect information on urine output given the retrospective nature of the study, and less than one-half of the cohort was located in the ICU.

In conclusion, this study suggests that the duration of TZP therapy is not associated with nephrotoxicity in patients with GNB. Baseline SCr, total body weight and vasopressor use were the only factors independently associated with nephrotoxicity.

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Competing interests

RGH has participated on an advisory board for Genentech and has received grant funding from Merck. All other authors declare no competing interests.

Ethical approval

Ethical approval for this study was received from the Texas Health Resources Institutional Review Board [IRB no. Pro 3313] and Texas Tech University [HSC IRB: A11-3689].

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