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INFECTIOUS DISEASES | RESEARCH ARTICLE

Evaluating the clinical outcomes associated with a modified prolonged infusion piperacillin–tazobactam protocol: A pilot study

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Abstract: *Purpose*: This study evaluated the clinical outcomes of a hospital-wide initiative of a 4-h prolonged infusion piperacillin–tazobactam (pip–tz) vs. a 30-min and a 4-h prolonged infusion. *Methods*: This retrospective study included patients who received pip–tz by two different infusion models with a documented or suspected Gram-negative infection. Patients can receive a 30-min infusion then a 4-h infusion or a 4-h infusion of pip–tz. The study's primary outcomes were length of stay (LOS) and 30-day mortality. *Findings*: Seventy-four patients received both types of infusion (SP) and 275 patients received only the prolonged infusion (PI). Using univariate analysis, the PI group had a higher mortality rate (13%) vs. SP group (4%) ($p = 0.033$). The PI group had a higher mean LOS (12.6 ± 9.5 days) vs. the SP group (10.3 ± 8.2 days) ($p = 0.04$). The type of infusion was not a significant predictor of LOS or mortality in multiple regression analysis ($p > 0.05$). *Implications*: This preliminary study showed that the PI group had a higher mortality rate and LOS compared to the SP group. However, this finding was not replicated using multiple regression analysis probably due to small sample sizes. Further studies using larger samples are warranted to clarify the clinical effectiveness of the different practices of prolonged infusion piperacillin–tazobactam.

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Lee H. Nguyen is an assistant professor at Loma Linda University School of Pharmacy with a clinical practice site at St. Jude Medical Center. He is the co-head of the Antimicrobial Stewardship Program at St. Jude Medical Center. The goal of the stewardship program is to ensure that all patients with infections receive optimal antimicrobial therapy. Prolonged infusion of piperacillin–tazobactam was adopted as part of the stewardship program. Research topics of interest are related to the stewardship program and impact of the program. The research study titled, "Evaluating the Clinical Outcomes Associated with a Modified Prolonged Infusion piperacillin–tazobactam Protocol: A Pilot Study," was performed to assess the impact on patient care and patient safety. The impact of initiating prolonged infusions is an unknown factor that may possibly improve patient care. The stewardship program will continue to evaluate the prolonged infusion process. Future directions include expanding prolonged infusions to other antibiotics.

PUBLIC INTEREST STATEMENT

Use of piperacillin–tazobactam is one of the most common treatment modalities for a suspected or confirmed Gram-negative infection. The increased concern for resistance with limited new antibiotics and attempts to improve patient care has led to the adoption of prolonged infusion of piperacillin–tazobactam as common practice. The adoption of prolonged infusion of piperacillin–tazobactam was done due to mathematical modeling and not randomized clinical trials. The majority of previous prolonged infusion studies have been retrospective in nature. Maximizing the pharmacokinetic and pharmacodynamic parameters of piperacillin–tazobactam is thought to improve clinical outcomes, but without blinded clinical trials, there can be only suggestions of benefit. Knowledge areas still missing from implementing prolonged infusion are how therapy should be initiated and when prolonged therapy should be started. This lack of data represents areas of potential improvement of patient care. Any additional data will only prove benefit to the use of piperacillin–tazobactam as a prolonged infusion.

Subjects: Acute Care; Infectious Diseases; Public Health Policy and Practice

Keywords: piperacillin–tazobactam; mortality; infusion

1. Introduction

The growing acceptance of prolonged infusion of piperacillin–tazobactam has been well documented (Lodise, Lomaestro, & Drusano, 2007; Patel et al., 2009; Xamplas et al., 2010; Zvonar & Kanji, 2010). Utilizing prolonged infusions capitalizes on the pharmacodynamic profile of beta-lactams to enhance their effectiveness (Falagas, Tansarli, Ikawa, & Vardakas, 2013; Lomaestro & Dursano, 2002). Prolonged infusion of piperacillin–tazobactam decreased mortality and hospitalization rates in critically ill patients with Pseudomonas aeruginosa infections (Lodise et al., 2007).

The utilization of a prolonged piperacillin–tazobactam infusion protocol can be very alluring to many institutions because of the cost-saving potential (Heinrich et al., 2011; Kaufman, Donnell, & Hickey, 2011; Xamplas et al., 2010). Several studies have documented the benefits of prolonged infusions of piperacillin–tazobactam and its impact on patient care (Dow, Rose, Fox, Thorpe, & Fish, 2011; Falagas et al., 2013; Lodise et al., 2007; Patel et al., 2009; Yost & Cappelletty, 2011). The practicality of 4-h infusions in the emergency department (ED) could possibly limit the ability to effectively treat patients in dire need of other emergency medications due to the incompatibility of piperacillin–tazobactam with medications such as dobutamine, amiodarone, and pantoprazole (Trissel, 2013). The newer formulation of piperacillin–tazobactam that contains ethylenediaminetetraacetic acid is only compatible with a limited number of medications (Trissel, 2013; Zosyn (R) [Package Insert]. Pfizer Inc., 2013) Examples would include emergency situations where only a single intravenous (IV) catheter access is available or catheter dislodgement resulting in single IV line access. As a result of this concern, a modified prolonged piperacillin–tazobactam infusion protocol was developed at St. Jude Medical Center, Fullerton, CA. All patients coming to the ED or intensive care unit (ICU) for medical treatment, where IV line access is problematic, can receive a 30-min infusion of piperacillin–tazobactam prior to a prolonged (4-h) infusion after 6-h. Using a 30-min infusion instead of a 4-h infusion allows for greater intravenous line access for other intravenous medications that need to be given but are incompatible with piperacillin–tazobactam. The 30-min infusion also allowed for greater acceptance of the prolonged infusion protocol. The original proposal was to have a 30-min infusion in the ED or ICU ward, followed by a second dose within 2–3 h. The original proposal was dismissed because limited clinical information was known about the best practices for prolonged infusions, and thus acceptance of the protocol was not unanimous. One concern of using prolonged infusion was the impact it would have on patient survival based on sufficient drug levels within the first few hours of antibiotic administration (time to appropriate). When antibiotics were given within one hour of triage, there can be a 7% improvement in survival (Gaieski et al., 2010). The rate of survival drops with every hour of delay in antibiotic administration (Siddiqui, Salahuddin, Raza, & Razzak, 2009).

Currently, there is no standard method of when to implement a prolonged infusion of piperacillin–tazobactam (Fahimi et al., 2012; Lau et al., 2006; Lee, Liou, Yee, Quan, & Neldner, 2012; Lorente et al., 2009; Rafati et al., 2006), and there is no standard methodology of how the first dose or first few doses should be given. Consequently, there is a wide variability in the dosing and timing of prolonged infusion of piperacillin–tazobactam in practice.

2. Aim and objectives of the study

The aim of the study is to evaluate the clinical effect (e.g. length of hospitalization and 30-day mortality) of two different prolonged infusion methods for piperacillin–tazobactam at St. Jude Medical Center. The specific objectives of the study are to:

(1) Describe the characteristics of patients in each group,

(2) Determine and compare the clinical outcomes of a 30-min infusion prior to a prolonged infusion and after a prolonged infusion, and

(3) Determine the significant predictors of length of stay (LOS) and mortality.

3. Methods

Loma Linda University Institutional Review Board and the St. Jude Medical Center Institutional Review Board approved this study. This study was conducted at St. Jude Medical Center, a 384-bed community hospital in Fullerton, CA. In October 2011, St. Jude Medical Center implemented a 4-h prolonged piperacillin–tazobactam infusion protocol where all patients would receive 3.375 g every 8-h or less frequently depending on renal function (Patel, Scheetz, Drusano, & Lodise, 2010). The protocol was modified in the ED and the ICU where piperacillin–tazobactam (pip–tz) 3.375 g could be given as a short infusion over 30-min for the first dose. All subsequent doses would be a prolonged 4-h infusion. This method of infusion was denoted as the SP option. The rationale was to provide patients with sufficient concentrations of pip–tz, early, and to provide intravenous line access to other medication. All patients who received the 4-h infusion empirically were denoted as the PI option.

During the month of October 2011, patients were transitioning to prolonged infusion therapy and quality improvement evaluations were done to ensure all pumps were programmed to infuse pip–tz over 4-h. The quality improvement period ended in the middle of November. Pharmacy utilization data were used to identify all patients (>17 years old) admitted to the hospital between 1 November 2011 and 1 December 2012. All patients with a suspected or documented Gram-negative infection based on ICD-9 coding and received five days or more of piperacillin–tazobactam were evaluated for inclusion to the study. Five days of therapy were arbitrarily selected because most microbiology cultures typically have preliminary results with 48–72 h and all cultures are finalized by the fifth day. Patients with piperacillin–tazobactam resistant cultures would typically be identified and subsequently the therapy would be modified within the first five days of starting piperacillin–tazobactam administration. The SP patients received their first dose of piperacillin–tazobactam as a 30-min infusion followed by a 4-h prolonged infusion of the same antibiotic within 6 h. The PI patients consisted of patients who only received the 4-h infusion of piperacillin–tazobactam for their infections.

Medical charts were reviewed for pertinent demographic, laboratory, and clinical data. Patient data included age, gender, co-morbid conditions, residence prior to hospitalization (home, transferred from outside hospital or facility), source of infection, ICU, and length of stay (LOS). Co-morbid conditions evaluated included presence of malignancy, heart failure, diabetes mellitus, and HIV status. An Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated for each patient at the time pip–tz was initiated to assess the severity of underlying illness (Knaus, Draper, Wagner, & Zimmerman, 1985). Additionally, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to identify patients with infections (Figure 1). All patient records/information were anonymized and de-identified prior to analysis. Data were collected using a data collection form and were entered in Microsoft Excel®.

3.1. Statistical analysis

Descriptive statistics (e.g. mean, frequencies, standard deviation, and median) were computed for all study variables that were measured on an interval or ratio scale. Discrete data were presented as frequencies and percentages. The student *t*-test was used to compare mean Acute Physiology and Chronic Health Evaluation II [APACHE II] score differences and other continuous variables by the type of infusion received. The Pearson's chi-square or Fisher's test was used to measure the association between dichotomous variables (e.g. presence or absence of a co-morbid condition and previous antibiotic use). All tests were two tailed and a p-value of ≤ 0.05 was considered significant. Bivariate regression was used to identify all significant predictors of mortality (logistic) and LOS (linear). Mortality was defined as all-cause mortality of hospitalized patients expiring within 30 days after starting the antibiotic regimen. Multiple logistic regression and multiple linear regression were used to regress mortality and the LOS, respectively, on those independent variables that were found to be significant predictors of mortality and LOS in bivariate analyses. Statistical analyses were carried out with SPSS version 20.0 (Chicago, IL, USA) and GraphPad Prism version 6.0 (San Diego, CA, USA).

4. Results

During the study period, there were 2,587 orders for piperacillin–tazobactam of which only 1,370 were non-duplicate patients and received the 4 h infusion. Nine hundred and twenty-nine patients were excluded because they received less than five days of therapy. Another 92 patients were excluded from the study due to the lack of an ICD-9 code for infection. In total, there were 349 patients who were included in the study (Figure 1). Seventy-four patients received both a short and prolonged infusion of pip–tz. There were 275 patients that received only prolonged infusions of pip–tz. There was no statistically significant difference in the age, gender, ethnicity, residence, co-morbid conditions, APACHE II scores, concomitant fluoroquinolone or aminoglycoside/colistin or pip–tz dosing regimen between the two groups (Table 1). However, more patients in the treatment option PI group were admitted to the ICU floors and were more likely to have received vancomycin concomitantly ($p < 0.05$).

The study patients represented an elderly population (mean ± SD, 65.6 ± 19.1 years) with moderately severe underlying illness (mean ± SD APACHE II scores, 14.66 ± 8.6). The two main differences between the PI and SP groups were the ICU admission (43.6% vs. 28.4%) and the utilization of vancomycin (63.6% vs. 50%), respectively. Baseline microbiology for culture positive Gram-negative bacteria was relatively similar between the two groups (SP; 57% vs. PI; 53%, $p = 0.57$) with one exception (Table 1). The SP group had a higher prevalence of Gram-negative bacteria in intra-abdominal cultures than the PI group (16% vs. 3%, $p < 0.0001$). Table 1 lists the ICD-9-CM diagnoses of the infectious processes in both groups. Two infectious processes were statistically different between the groups. The SP treatment group had a higher rate of intra-abdominal infections (36% vs. 14%) and lower levels of pneumonia (35% vs. 70%) when compared to the PI group.

The study evaluated the effect of a modified prolonged infusion protocol on 30-day mortality and the total duration of hospitalization/LOS. The SP treatment group ($n = 3$, 4%) had a statistically significant lower mortality rate (univariate analysis) when compared to the PI group ($n = 35$, 13%),

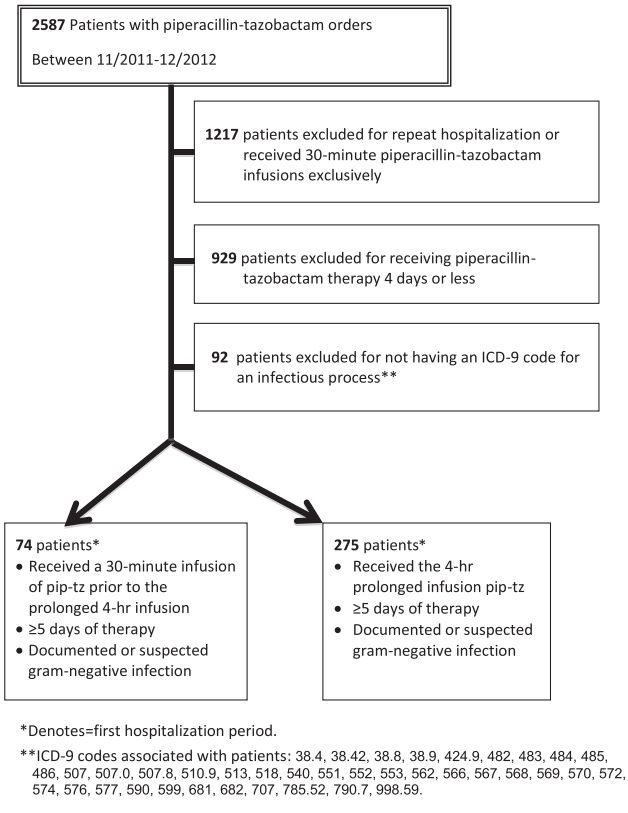

Figure 1. Flowchart of study population.

Table 1. Patient demographics

Variables	SP option, *N* = 74	PI option, *N* = 275	*p*-Value
Age (years)			
Mean ± SD	65.6 (19.1)	68.7 (16.5)	0.211
Gender			
Male	40 (54%)	145 (53%)	0.839
Ethnicity			
Caucasian	48 (65%)	194 (71%)	0.530
African-American	0 (0)	3 (1%)	
Hispanic	10 (13%)	34 (12%)	
Asian	16 (22%)	44 (16%)	
Admitting residence			
Home	68 (92%)	241 (88%)	0.594
Skilled nursing facility	5 (7%)	28 (10%)	
Outside hospital	1 (1%)	6 (2%)	
Admission location			
Intensive care unit	21 (28%)	120 (44%)	0.018
Concomitant antibiotic use			
Fluoroquinolones	29 (39%)	126 (46%)	0.308
Aminoglycoside/colistin	2 (3%)	7 (2%)	0.940
Vancomycin	37 (50%)	175 (64%)	0.033
Other agent	3 (4%)	7 (2%)	0.699
Co-morbid conditions			
Malignancy	15 (20%)	73 (26%)	0.270
Heart failure	9 (12%)	53 (19%)	0.155
Diabetes mellitus	16 (22%)	84 (30%)	0.132
History of healthcare exposure	20 (27%)	92 (33%)	0.293
History of antibiotic use (30-d)	4 (5%)	28 (10%)	0.206
APACHE II score, mean ± SD	14.66 (8.6)	16.64 (8.7)	0.082
Onset of infection, ICU	3 (4%)	49 (18%)	0.003
GPC co-infection	26 (35%)	111 (40%)	0.414
Yeast co-infection	19 (26%)	80 (29%)	0.563
Culture positive, GNR (Total)	42 (57%)	146 (53%)	0.57
Respiratory tract	6 (8%)	28 (10%)	0.593
Urinary tract	13 (18%)	57 (21%)	0.547
Skin/skin structure	2 (3%)	18 (6%)	0.207
Intra-abdominal	12 (16%)	9 (3%)	<0.0001
Bacteremia	8 (11%)	25 (9%)	0.654
Other	1 (1%)	9 (4%)	0.695
Dosing regimens			
3.375 gm IV Q 8-h	65 (87.8%)	230 (83.6%)	0.408
3.375-gm IV Q 12-h	7 (9.5%)	40 (14.5%)	0.251
3.375-gm IV Q 6-h	1 (1.4%)	1 (0.36%)	0.381
Other*	1 (1.4%)	3 (1.1%)	1
Pip-tz treatment days, mean ± SD	7.42 (3.1)	7.64 (3.15)	0.592

(*Continued*)

Table 1. (*Continued*)

Variables	SP option, *N* = 74	PI option, *N* = 275	*p*-Value
Infections based on ICD-9			
Pneumonia	26 (35%)	174 (70%)	<0.0001
Bacteremia	31 (42%)	95 (34%)	0.243
Skin/skin structure infections	3 (4%)	14 (5%)	0.713
Intra-abdominal infections	27 (36%)	39 (14%)	<0.0001
Cystitis/pyelonephritis	8 (11%)	16 (6%)	0.132
Osteomyelitis/prosthetic Infections/endocarditis	3 (4%)	8 (3%)	0.617
Other	6 (8%)	19 (7%)	0.723
Patients with >1 infection source**	28 (38%)	84 (30%)	0.233

Notes: GPC—Gram-positive cocci; GNR—Gram-negative rods.

*Other dose: 4.5 and 2.25 g IV Q 8-h.

**Patients with mixed infections (SP, *n* = 28; PI, *n* = 84); ICD-9 Codes (Figure 1): osteomyelitis/prosthetic infections/endocarditis not likely source of primary Gram-negative infection but part of the overall infectious problem identified with ICD-9 codes.

Table 2. Multivariate analyses: mortality

Variables	Study group		
	Adj. O.R.	95% C.I.	*p*-Value
Infusion type	0.30	0.07–1.45	0.116
Concomitant vancomycin	2.57	0.22–29.9	0.452
Co-morbid conditions			
Heart failure	1.25	0.43–3.62	0.678
Diabetes mellitus	2.25	0.86–5.87	0.097
Malignancy	0.16	0.07–0.39	<0.0001
ICU admission	0.73	0.27–2.00	0.539
Onset of infection, ICU	0.3	0.12–0.79	0.015
APACHE II scores	1.13	1.07–1.19	<0.0001
Infections types			
Pneumonia	1.08	0.39–3.00	0.881
Intra-abdominal infection	1.62	0.36–7.20	0.529

$p = 0.033$. The total LOS in the SP group (10.3 ± 8.2 days, SD) was less than that in the PI group (12.6 ± 9.5 days, SD), $p = 0.04$ (univariate analysis).

4.1. Predictors of mortality and LOS (multivariate analysis)

The type of infusion was not a statistically significant predictor of mortality rate, [adjusted odds ratio (OR) 0.3; 95% confidence interval (CI) 0.07–1.45]. Mortality was predicted by malignancy, location of onset of infection (ICU), and APACHE II scores (Table 2).

The statistically significant predictors of LOS were concomitant vancomycin/Gram-positive cocci infection, fluoroquinolone use, ICU onset of infection, APACHE II scores, concomitant yeast infection, mechanical ventilation, and malignancy ($p < 0.05$). Infusion type was not a statistically significant predictor of LOS.

5. Discussion

This study examined effects of a modified prolonged infusion piperacillin–tazobactam protocol on mortality and LOS at a community hospital. Study results show that patients who received the 30-min infusion prior to the prolonged infusion of piperacillin–tazobactam had statistically significantly lower rates of mortality, 4% vs. 13%, and a shorter hospitalization period, 10.3 days vs. 12.6 days. This suggests that our hospital's SP infusion protocol is at least as clinically effective as the 4-h prolonged infusion of piperacillin–tazobactam commonly used in practice.

However, after controlling for confounders, the type of infusion (SP vs. PI) did not have an effect on mortality in the logistic regression model. In addition, in the linear regression analysis, the type of infusion did not significantly predict LOS after controlling for confounders.

Since its implementation, the prolonged infusion of pip–tz has been widely accepted by medical professionals at our hospital. All utilization and mortality data were presented to the pharmacy and therapeutics committee, which supported the continuation of the current protocol with ICU and the ED having the availability to infuse the first dose of pip–tz over 30 min. Since the inception of the prolonged infusion protocol, the comfort level of starting patients on prolonged infusion has increased hospital wide. The ED at our hospital continues to infuse the first dose of pip–tz over 30 min due to line access issues, but the ICU patients typically will have multiple intravenous access allowing for either short or prolonged infusions of pip–tz.

Our study has several limitations. First, the retrospective design limits the assessment of every variable that can potentially influence the outcome. Variables were not collected regarding minimum inhibitory concentrations, but it is unknown what pathogens were identified to cause the infection. Other variables that were not collected include viral co-infections, other co-morbid conditions that may prolong hospitalization, and time to clinical stability or success. The number of patients with culture positive Gram-negative rods was not different between the two groups, but a larger study would allow for better generalization of the effectiveness of the treatment options. Second, patients included in the study were not randomized into two groups. There is an inherent bias of selection for the two groups. The lack of multiple intravenous access in the ED predisposed this group to more likely receive the short infusion therapy first. This was also true of patients who received prolonged infusion in the ICU. Patients in the ICU are more likely to have multiple line access and can receive a prolonged infusion of pip–tz as a first dose. It is therefore possible that the results could be due to chance. However, the two groups did have similar demographics in most respects such as APACHE II scores when pip–tz was initiated, co-morbid conditions, and similar number of positive microbiologic cultures with the exception of intra-abdominal infections. The other differences between the groups were the onset of infection location, concomitant vancomycin utilization, and ICD-9 code for pneumonia and intra-abdominal infections.

Third, was the arbitrary inclusion of patients who received five days or more of piperacillin–tazobactam. The basis for five days of piperacillin–tazobactam is that all positive cultures that were piperacillin–tazobactam resistant would have been changed prior to day five of therapy. Including patients with a minimum of five days of therapy limited the pool of patients as well as how piperacillin–tazobactam was truly utilized in clinical practice. This may have introduced selection bias. Fourth, the study had a small sample size and was underpowered, especially to multivariate analyses. A *post hoc* sample calculation on mortality was performed and revealed a power of 62.1%. LOS had a *post hoc* power of 54.3%. This may explain the non-significant relationship between infusion type and the primary clinical outcomes.

6. Conclusion

With the growing acceptance of prolonged infusions, evaluating differences in approaches to this type of therapy is needed to determine safety and efficacy. Currently, there is no consensus on when

to initiate a prolonged infusion of piperacillin–tazobactam. This preliminary investigation describes the clinical effectiveness of two methods of initiating prolonged infusion of piperacillin–tazobactam currently utilized at our hospital.

The study findings show that patients in the PI group had higher mortality rate and LOS compared to those in the SP group, suggesting that the hospital's protocol is at least as clinically effective as the 4-h prolonged infusion of piperacillin–tazobactam. However, this finding was not replicated using multiple regression analysis probably due to the small sample size. Further studies using larger samples and stronger study designs are warranted to clarify the clinical effectiveness of the different practices of prolonged infusion of piperacillin–tazobactam.

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Competing interests
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