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A Community Hospital Antimicrobial Stewardship Program's Assessment of Prolonged Infusion Piperacillin-tazobactam for Pseudomonas Aeruginosa Pneumonia

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Research

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Abstract

Background: The study aim was to determine and compare the length of hospitalization, mortality, clinical stability, and time to clinical stability of a standard infusion (SI) and prolonged infusion (PI) piperacillin-tazobactam (TZP) in *Pseudomonas aeruginosa* (PA) pneumonia patients.

Methods: This retrospective study evaluated length of hospitalization, mortality, clinical stability, and time to clinical stability with either SI-TZP or PI-TZP therapy in hospitalized patients diagnosed with PA pneumonia between January 01, 2008 and June 30, 2014. Patients were included in the study if they received ≥2 days of TZP, were diagnosed with PA pneumonia, and had TZP therapy initiated within 3 days of the documented PA infection.

Results: A similar proportion of patients achieved clinical stability between the PI (n=14, 70%) and SI (n=22, 67%) groups, (p=0.8). There was no statistically significant difference in the average time to clinical stability between the PI (mean=5.3±3.6) and SI (mean=5.8±6.8) groups, (p=0.77). The total length of stay in the PI group (mean=15.9±9.8) was shorter than in the SI group (mean=23.9±33) but did not achieve statistical significance, p=0.2. The 14-day all-cause mortality was similar between the two groups, PI (n=1, 5%) and SI (n=2, 6%).

Conclusion: The use of PI TZP was equally effective as standard therapy. Further research is warranted to confirm these findings on the clinical benefits of prolonged infusion therapy.

Introduction

Many hospital antimicrobial stewardship programs are increasingly using piperacillin-tazobactam as a prolonged infusion (PI).[1-7] Similar to other beta-lactam antibiotics, piperacillin-tazobactam (TZP) is concentration independent.[8] Its antibacterial effects are optimized when the concentration of TZP exceeds the minimum inhibitory concentration of the bacterial organism for at least 50% of the dosing interval.[5] Common prolonged infusion TZP utilizes either 3.375 grams or 4 grams infused over 4 hours every 8 hours, whereas standard infusions (SI) of TZP are infused over 30 minutes every 6 hours. The desired result common among all hospital stewardship programs that implement prolonged infusions is improved patient outcomes while utilizing less TZP.

Several studies evaluated prolonged infusion of TZP [2-5, 7, 9] and reported a mix of improved mortality rates or no difference in treatment outcome.[1-3, 7] The majority of the studies were focused on treating gram-negative infections, with few focusing on treating *Pseudomonas aeruginosa* (PA)

infections. *Pseudomonas aeruginosa* infections are more difficult to treat compared to other gram-negative pneumonias such as E. coli because of the higher minimum inhibitory concentrations seen in PA.[10] Using prolonged infusions to maximize TZP exposure in sicker patients with PA pneumonia (Acute Physiological and Chronic Health Evaluation II scores ≥17) have been shown to reduce mortality. Other potential benefits found were shorter hospital/intensive care length of stay, fewer days on a ventilator, and reduced acquisition cost compared to standard infusions of TZP.[1, 11]

Currently, there is limited data on the use of prolonged infusion TZP in PA infections.[3] There is also limited information regarding the effects of prolonged infusion on achieving clinical stability and time to clinical stability in patients with PA pneumonia. The aim of this study was to evaluate the clinical effect (e.g., clinical stability and time to clinical stability) of prolonged infusion of TZP compared to standard infusion in the treatment of PA pneumonia. The specific objectives of the study were to: 1) Determine and compare the length of hospitalization and mortality of standard and prolonged infusion of TZP in PA pneumonia patients, and 2) Determine and compare clinical stability and time to clinical stability of standard and prolonged infusion of TZP in PA pneumonia patients.

Prolonged infusion of TZP was approved by the Pharmacy and Therapeutics Committee and hospital-wide conversion was initiated on November 1, 2011. One of the key components to institutional acceptance of prolonged infusion was garnering the support from the heads of the different departments that had high utilization of TZP, including internal medicine and intensivists. Prolonged infusion therapy is not a new concept, and providing information about which local and national institutions have adopted this type of therapy and the rationale of prolonged infusions diminished concerns of deploying nontraditional TZP infusions. Another main component of programmatic success was the hospital-wide use of electronic infusion pumps. All the infusion pumps were reprogramed with a default TZP infusion rate of 13.75 mL/hr, which equates to a 4 hour infusion. If a patient required a 30-minute infusion of TZP, the infusion rate needed to be entered manually. Lastly, providing education to the nursing and pharmacy staff regarding infusion times, dosing adjustments, and compatibilities issues was necessary to avoid potential medication errors.

Prior to November 1, 2011, all patients received standard 30-minute infusions of TZP, and after the implementation date, all patients received prolonged 4 hour infusions of TZP. The multiple strengths (2.25, 3.375, and 4.5 grams) and dosing frequencies of TZP were consolidated into a simpler format with prolonged infusion . The institution adopted two major formats for administering prolonged infusion of TZP. It is available as 3.375 grams every 8 hours or 3.375 grams every 12 hours for patients with a creatinine clearance of less than 20 ml/min. Hemodialysis patients received 3.375 grams every 12 hours but with a 30-minute infusion. During the evaluation period prior to implementing the prolonged infusion protocol, the available microbiology records indicated that the majority of Pseudomonas aeruginosa had a minimum inhibitory concentration (MIC) of 8 mg/L. A 4 hour infusion of 3.375 grams of TZP has a >90% probability of attaining the target of 50% free drug exceeding the MIC.[12]

Methods

The St. Jude Medical Center Institutional Review Board approved this retrospective chart-review study. This study evaluated all patients with PA pneumonia that were hospitalized between January 01, 2008 and June 30, 2014. Patients were selected for inclusion in the study if they received ≥2 days of TZP, were diagnosed with PA pneumonia based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 482.1 , and had TZP therapy initiated within 3 days of the documented PA infection. Patients were excluded from the study if they had isolated a PA resistance to TZP, received concomitant effective beta-lactam therapy for the PA pneumonia, were diagnosed with cystic fibrosis, or were on hemodialysis. Pharmacy utilization records were used in conjunction with ICD-9 codes to identify which patients had PA pneumonia and utilization of TZP. If PA pneumonia and TZP utilization were isolated on multiple occasions during the study period, only the first episode of infection was reviewed. Each patient record was evaluated to determine inclusion or exclusion from the study.

Medical charts for the included patients were reviewed for pertinent demographic, determination of TZP infusion type, laboratory, microbiology information, and clinical data to determine clinical stability. Patient data included age, gender, comorbid conditions, intensive care unit (ICU) admission, mechanical ventilation, length of stay (LOS), onset of infection location, Pseudomonas aeruginosa MICs, and in-hospital mortality. Mortality was defined as all-cause mortality of hospitalized patients expiring within 14 days after starting the antibiotic regimen. Comorbid conditions evaluated included presence of malignancy, chronic kidney disease, diabetes mellitus, and chronic obstructive pulmonary disease. A Charlson Comorbidity Index (CCI) score was calculated at the time TZP was initiated to quantify the number of comorbid conditions and risk of mortality.[13] Each comorbid condition was identified through medical charts. Primary endpoints evaluated were clinical stability and time to clinical stability. Clinical stability was defined as heart rate ≤100 beats/min, systolic blood pressure ≥90 mm Hg, respiratory rate ≤24/min, oxygen saturation ≥90%, and temperature ≤37.2°C. Time to clinical stability was defined as the number of days required for clinical stability parameters to return to normal values for more than 24 hours since TZP initiation. Secondary endpoints evaluated were all-cause in-

Table 1. Demographic Information of the Patients

Characteristics	PI (n=20)	SI (n=33)	P-value
Age (years), median (IQR)	75 (53-79)	69 (64-79)	0.71
Gender			
Male, No. (%)	11 (55)	18 (55)	0.97
Female, No. (%)	9 (45)	15 (45)	
Ethnicity, No. (%)			
White	13 (65)	25 (75.8)	0.4
Others	7 (35)	8 (24.2)	
Residence, No. (%)			
Home	16 (80)	22 (66.7)	0.35
SNF or OSH	4 (20)	11 (33.3)	
Comorbidities, No. (%)			
Diabetes Mellitus	5 (25)	5 (15.2)	0.47
COPD	6 (30)	13 (39.4)	0.49
Cancer	6 (30)	7 (21.2)	0.47
Chronic Kidney Disease	3 (15)	2 (6.1)	*
CCI Score, median (IQR)	5 (3.8-7)	5 (4-6)	0.92
Number of comorbidities, median (IQR)	2 (0.8-4)	1 (1-2)	*
Concomitant antibiotics, No. (%)			
Fluoroquinolones	5 (25)	20 (60.6)	0.02
Aminoglycosides	8 (40)	8 (24.2)	0.23
Onset of infection, ICU	10 (50)	14 (42.4)	0.59
Mechanical ventilation, No. (%)	14 (70)	18 (54.5)	0.26
Days on mechanical ventilation, mean ±SD	16.4±10.3	13.7±13.6	0.51
CrCl (ml/min), No. (%)			
CrCl >50	12 (60)	27 (81.8)	0.08
CrCl 21-50	5 (25)	4 (12.1)	0.27
CrCl ≤20	3 (15)	2 (6.1)	*
Duration of therapy (days), mean ±SD	8.4 ±4.3	8.3 ±7.9	0.99
Treatment regimens, No. (%)			
2.25 grams every 6 hours	0 (0)	5 (15.2)	*
3.375 grams every 6 hours	0 (0)	19 (57.6)	*
3.375 grams every 8 hours	16 (80)	9 (27.3)	0.0002
3.375 grams every 12 hours	3 (15)	0 (0)	*
4.5 grams every 8 hours	1 (5)	0 (0)	*
Average TZP gram per patient per day	9.8	11.9	

*Indicates that data cells in one or more cells is too small (<5) to allow the computation of P-value

TZP: piperacillin-tazobactam, PI: prolonged infusion, SI: standard infusion, SNF: skilled nursing facilities, OSH: outside hospital, COPD: chronic obstructive pulmonary disease, CCI: Charlson Comorbidity Index, IQR: interquartile range, CrCl: creatinine clearance estimated by Cockcroft-Gault

Table 2. Primary Outcomes of the Patients

	PI (n=20)	SI (n=33)	P-value
Achieved clinical stability, No. (%)	14 (70)	22 (66.7)	0.80+
Time to clinical stability (days), mean ±SD	5.3 ±3.6	5.8 ±6.8	0.77+
Hospital LOS (days), No. (%)			
Post-culture, mean ±SD	11.5 ±6.3	19.8 ±33.0	0.17+
Total, mean ±SD	15.9 ±9.8	23.9 ±33.0	0.20+
Mortality, 14-day (all-cause), No. (%)	1 (5)	2 (6.1)	*

*Indicates that data cells in one or more cells is too small (<5) to allow the computation of P-value, +independent t-test

LOS: length of stay

hospital 14-day mortality and LOS.

Data Analysis

Descriptive statistics were computed for all study variables that were measured on an interval or ratio scale. Discrete data were presented as frequencies and percentages. The independent student t-test was used to compare mean CCI score differences, LOS, number of patients who achieved clinical stability, and the average time to clinical stability by the type of infusion received. Either Pearson's chi-square test or Fisher's test was used to measure the association between dichotomous variables. All tests were two-tailed and a P-value of <0.05 was considered significant. Statistical analyses were carried out with SPSS version 20.0 (Chicago, IL, USA) and GraphPad Prism version 6.0 (San Diego, CA, USA).

Results

During the study period, 122 patients were identified as having PA pneumonia. Fifty-three patients with a median age of 72 (SD±15.1) years met the inclusion criteria and were included in the study. Twenty patients received standard infusions of TZP and 33 patients received prolonged infusions of TZP. The majority of the patients were men (55%) and Caucasian (72%) who resided at home (72%) prior to hospitalization. Baseline characteristics are listed in Table 1.

The demographics of the two groups did not differ, with the exception of concomitant fluoroquinolone utilization (PI: 25% vs SI: 61%, p=0.02), and type of TZP infusion. Table 1 lists different treatment regimens used for the Pseudomonas pneumonias. The most common regimen of the PI group was 3.375 grams every 8 hours (n=16, 80%) with 3.375 grams every 6 hours (n=19, 58%) as the most common regimen in the standard 30-minute infusion group. The average amount of TZP utilized was lower in the PI group, (9.8 grams vs 11.9 grams). There was no difference in duration of therapy (mean days ±SD) between the two groups (PI: 8.4±4.3 vs SI: 8.3±7.9, p=0.99).

There was no statistically significant difference in the proportion of patients in the prolonged infusion group (n=14, 70%) and the short infusion group (n=22, 67%) who achieved clinical stability (p=0.8; Table 2). The PI group (n=2, 10%) had a lower number of patients who were clinically stable at onset of TZP therapy compared to the SI group (n=10, 30%). When excluding the number of patients that were clinically stable at the onset of TZP therapy, the PI group (n=12, 60%) had higher rates of achieving clinical stability compared to the SI group (n=12, 36%) but did not reach significance, p=0.09. There was no statistically significant difference in the mean time to clinical stability days between the PI group (mean = 5.3±3.6) and the SI group (mean = 5.8±6.8, p=0.77). The total LOS (mean days ±SD) in the PI group (15.9 ±9.8) was shorter than the SI group (23.9 ±33) but did not achieve statistical significance, p=0.2. The 14-day all-cause mortality was similar between patients in the PI group (n=1, 5%) and those in the short infusion group (n=2, 6%).

The distribution of MICs can be seen in Table 3. The most common MIC in each group was 8 mg/L (PI: 79% vs SI: 48%). The SI group had a larger proportion of patients with MICs >8 mg/L, (PI: 16% vs SI: 52%, p=0.03). Nine patients had susceptibilities performed using the Kirby-Bauer Disk Diffusion test and no MICs were available.

Discussion

This study evaluated the clinical outcomes associated with prolonged infusion piperacillin-tazobactam and standard infusion therapy for the treatment of Pseudomonas aeruginosa pneumonia. Study results show that patients who received prolonged infusions of TZP achieved similar rates of clinical stability to that of standard infusion, 70% vs 67%. Additionally, the time to clinical stability in the prolonged infusion group was similar to that of the standard infusion group, 5.3 days vs 5.8 days. This suggests that a 4 hour TZP infusion does not delay the time to clinical stability or limit the patients' ability to achieve clinical stability. The results of our study are similar to others in which the use of prolonged infusion of TZP was equally effective as standard therapy.[4,5,9] To our knowledge, this is the first study that evaluated prolonged infusion piperacillin-tazobactam for the treatment of Pseudomonas aeruginosa pneumonia and associated effects on clinical stability and time to clinical stability.

Table 3. Microbiology

Minimum Inhibitory Concentration (mg/L)	PI (N, %)	SI (N, %)
4	1 (5)	0
8	15 (79)	12 (48)
16	0	2 (8)
32	0	5 (20)
64	3 (16)	6 (24)

Nine patients did not have minimum inhibitory concentrations (PI: n=1, SI: n=8); Kirby-Bauer Disk Diffusion tests were used to determine susceptibility.

Similar mortality rates (5% vs 6%) and length of stay (16 days vs 24 days) were found between the two groups in this study, thus further supporting that prolonged infusion of TZP is as effective as standard infusion therapy for the treatment of Pseudomonas pneumonia. These results differ from those by Lodise et al , who showed mortality benefit in patients with elevated Acute Physiology and Chronic Health Evaluation and PA infections,[3] probably due to our smaller sample size (n=53 vs N=103 PA pneumonias), older patient population, and the fact that our evaluation was limited to PA pneumonia infections.

The main difference between the two groups was the amount of TZP utilized and the frequency of the infusions. On average the prolonged infusion group (9.8 grams) used less TZP than the standard infusion group (11.9 grams). Seventy-three percent of the SI group (n=24) received TZP doses every 6 hours, but the majority of the PI group (n=17, 85%) received TZP doses every 8 hours.

Our study has several limitations. First, several variables that may influence patient outcomes were not included on patient charts that were utilized for this study. These variables include other comorbid conditions or co-infections that may prevent clinical stability or delay time to clinical stability, such as cardiovascular disease. Consequently, the Charlson Comorbidity Index was used to capture the presence of 17 comorbid conditions,[13] but the conceded limitation is a potential incomplete capture of all possible comorbidity information. A second limitation is the small sample size. The small sample size is a consequence of looking at Pseudomonas pneumonia in a community hospital with carbapenems as the preferred agent, thus limiting the utilization of TZP. The antimicrobial stewardship program was formalized in the middle of 2011 and the majority of patients prior to 2011 received a carbapenem empirically for the treatment of Pseudomonas infections. Lastly, there is a discrepancy in the distribution of the Pseudomonas aeruginosa minimum inhibitory concentrations for TZP. In 2012, the Clinical and Laboratory Standards Institute (CLSI) lowered the susceptibility breakpoint from ≤64/4 mcg/mL to ≤16/4 mcg/mL. The lowered breakpoint introduced a potential selection bias with fewer patients in the prolonged infusion group having MICs higher than 8 mcg/mL.

As more institutions are considering the adoption of prolonged infusion TZP, the immediate consideration is efficacy compared to standard therapy. Current clinical evidence suggests that prolonged infusion of TZP has similar efficacy as standard infusions.[1-5, 7, 9, 11] Other considerations are the financial costs and impact on patient care. Using one less dose of TZP makes the process financially appealing. Standard amounts of TZP consumed ranges from 13.5-18 grams/day . Prolonged infusion of TZP would reduce the daily consumption to as little as 10.125 grams/day. Prolonged infusions may impact patient care on multiple levels. Piperacillin-tazobactam is incompatible with a various medications such as amiodarone, azithromycin, and pantoprazole.[14] The 4 hour infusion of TZP will limit other medications from being infused or would require a second intravenous access line. Prolonged infusion of TZP is also not ideal for patients in the emergency department. Having patients occupy a bed for 4 hours unnecessarily would be counterproductive in a fast-paced environment. Lastly, prolonged infusion of TZP therapy lasts 12 hours a day and will limit the activity of ambulatory patients.

Conclusion

As antimicrobial stewardship programs implement new ideas into practice, it is necessary to review and evaluate them to ensure patient safety. Currently, there is limited data on the benefit of prolonged infusion in Pseudomonas infections, with the exception of reduced antibiotic utilization. The study shows that patients receiving prolonged infusion had similar rates of achieving clinical stability and took similar amounts of time to clinical stability than those receiving standard infusion. The use of prolonged infusion of TZP was found to be equally effective as standard therapy. Further research using a larger sample is warranted to confirm these findings on the clinical benefits of prolonged infusion therapy.

About the Authors

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References

1. Brunetti L, P.S., Cunningham D, Toscani M, Nguyen J, Lim J, Ding Y, Nahass RG, *Clinical and Economic Impact of Empirical Extended-Infusion Piperacillin-Tazobactam in a Community Medical Center.* Ann Pharmacother, 2015. 49(7): pp. 754-60.
2. Lee GC, L.H., Yee R, Quan CF, Neldner K, *Outcomes of extended-infusion piperacillin-tazobactam: a retrospective analysis of critically ill patients.* Clin Ther, 2012. 34(12): pp. 2297-300.
3. Lodise TP, L.B., Drusano GL., *Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy.* Clin Infect Dis 2007. 44(3): pp. 357-63.
4. Lü Y, Y.Z., Wang DH, Dong WL, Yang Y, Xia R., *[Treatment study of hospital acquired pneumonia by optimizing dosing regimen of piperacillin/tazobactam:prolonged vs. regular infusion].* Zhonghua Wei Zhong Bing Ji Jiu Yi Xue, 2013. 25(8): pp. 479-83.
5. Patel GW, P.N., Lat A, Trombley K, Enbawe S, Manor K, Smith R, Lodise TP, *Outcomes of extended infusion piperacillin/ tazobactam for documented gram-negative infections.* Diagn Microbiol Infect Dis 2009. 64(236–40).
6. Xamplas RC, I.G., Glowacki RC, Grasso AE, Caquelin C, Schwartz DN, *Implementation of an extended-infusion piperacillin-tazobactam program at an urban teaching hospital.* Am J Health Syst Pharm 2010. 67(8): pp. 622-28.
7. Yost RJ, C.D., *The Retrospective Cohort of Extended-Infusion Piperacillin-Tazobactam (RECEIPT) study: a multicenter study.* Pharmacotherapy, 2011. 31(8): pp. 767-75.
8. Craig, W., *Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins.* Diagn Microbiol Infect Dis., 1995. 22(1-2): pp. 89-96.
9. Arnold HM, H.J., Skrupky LP, Smith JR, Juang PH, Hampton NB, McCormick S, Reichley RM, Hoban A, Hoffmann J, Micek ST, Kollef MH, *Prolonged infusion antibiotics for suspected gram-negative infections in the ICU: a before-after study.* Ann Pharmacother, 2013. 47(2): pp. 170-80.
10. Institute., C.a.L.S., *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Fifth Informational Supplement M100-S25.* 2015, CLSI: Wayne, PA.
11. Falagas ME, T.G., Ikawa K, Vardakas KZ, *Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin-tazobactam: a systematic review and meta-analysis.* Clin Infec Dis 2013. 56(2): pp. 272-82.
12. Lodise TP, L.B., Drusano GL. *Application of Antimicrobial Pharmacodynamic Concepts into Clinical Practice: Focus on B-Lactam Antibiotics. Insights from the Society of Infectious Diseases Pharmacists.* Pharmacotherapy, 2006. 26(9): pp. 1320–32.
13. Deyo RA, C.D., Ciol MA., *Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases.* J Clin Epidemiol., 1992. 45(6): pp. 613-9.
14. Trissel, L., *Handbook on Injectable Drugs (17th ed.).* 2013, Bethesda, MD: American Society of Health-System Pharmacists.