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System-Wide Implementation of the Use of an Extended-Infusion Piperacillin/Tazobactam Dosing Strategy: Feasibility of Utilization From a Children's Hospital Perspective

Kristen R. Nichols, Chad A. Knoderer, Elaine G. Cox, Michael B. Kays

Abstract

Background

Use of extended infusions of piperacillin/tazobactam (PT) in adult patients has been described, but data in children are limited.

Objective

The goal of this study was to determine the feasibility of using an extended-infusion PT dosing strategy as the standard of care in a children's hospital.

Methods

This was a prospective observational study of patients aged >30 days who received PT after admission to a freestanding, tertiary care children's hospital. After institution of an extended-infusion PT dosing protocol as the standard dosing option, patients receiving PT were prospectively assessed for presence of and reasons for changes in dosing regimen.

Results

A total of 332 patients, with a median age of 5 years (interquartile range, 1.9–12 years) and median weight of 19.9 kg (interquartile range, 11.7 – 37.6 kg) received PT (100 mg/kg based on piperacillin component). Extended-infusion PT was used for the duration of PT therapy in 92% (n = 304) of patients. Twenty-eight patients (8%) received a traditional infusion over 30 minutes, with 19 of 28 being changed from extended infusion and 9 of 28 being empirically prescribed traditional infusion PT. The most commonly encountered reason for not using extended infusions was coadministration of vancomycin (17 of 28 [61%]) and lack of compatibility data with PT. Dosing errors, which were voluntarily reported, were infrequent (1.8% [n = 6]). The few observed dosing errors were likely attributable to the overall ordering process at our institution, which requires ordering as the milligram per kilogram dose as total PT rather than based on piperacillin component as is commonly documented in pediatric dosing references.

Conclusions

Results of this study suggest that extended-infusion PT dosing was feasible in this specific children's hospital. Ninety-two percent of patients received our institution's preferred dosing regimen; a small percentage of patients still needed to receive traditional infusion times.

Introduction

Increasing prevalence of antimicrobial resistance is a growing issue encountered on a daily basis in hospitals caring for children.[1, 2, 3, 4, 5 and 6] Few alternative antibacterial agents are available to treat infections caused by multidrug resistant bacteria, primarily due to limited available pediatric tolerability and efficacy data and, ultimately, limited published experience with using such agents in pediatric patients. With developmental pharmacologic changes observed along the continuum of "pediatrics," simply extrapolating adult dosages to a pediatric patient is not always the safest or most effective approach.[7] Although detrimental effects on development have not been documented, there are few published data to establish optimal use, dose, and duration for alternatives to β-lactam antibacterial agents such as fluoroquinolones, aminoglycosides, tetracycline derivatives, and colistin. However, these medications may represent the entire antibacterial arsenal for the treatment of infections caused by resistant gram-negative bacteria in children, thereby requiring careful risk/benefit assessments. As with adult studies, pediatric studies have reported negative clinical outcomes associated with infections due to resistant bacteria, including increased length of stay and mortality.[2 and 8]

From a pediatric care perspective, it is critical to optimize the dosing of the currently available antibacterial agents based on drug-specific pharmacokinetic and pharmacodynamic parameters, thus increasing the probability that positive patient outcomes are maximized while minimizing the selective pressure for emergence of antibiotic resistance.[9 and 10] In general, β-lactam antibiotics and antibiotic combinations, such as piperacillin-tazobactam (PT), exhibit time-dependent bactericidal activity and, with the exception of carbapenems, minimal postantibiotic effects.[9] As a result, their pharmacodynamics are optimized by achieving a requisite length of time for which the free antibiotic concentrations remain above the MIC (fT > MIC) for the infecting organism. There is no apparent difference between adults and children with respect to these pharmacodynamic properties. Thus, any potential or proven benefits of optimizing pharmacodynamic exposures should apply to children as well as to adults.

Optimization of the PT bactericidal exposures can be achieved by increasing the dose while keeping the dosing interval the same, administering the same dose at more frequent intervals, administering the dose as a continuous infusion, or extending the duration of intermittent infusions.[11] Although there are certain pharmacokinetic differences observed between children and adults, the pharmacokinetic profiles of piperacillin and tazobactam, specifically $t_{1/2}$ values, reach adult values by 2 years of age.[7, 12 and 13] Doubling the dose of PT increases the fT > MIC by only ~1 $t_{1/2}$ of the medication.[14] Administering the medication at more frequent intervals would require 4-hour dosing intervals compared with 6-hour intervals, which may create a significant burden on nursing staff depending on the institution.

A potential solution is to use continuous or extended-infusion dosing strategies in children. Extended-infusion PT (EIPT) has been well described in adult patients, and many adult studies have evaluated the attainment of the target % fT > MIC by using Monte Carlo simulation.[11, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25] Lorente et al [26] reported superior clinical cure in ventilator-associated pneumonia with continuous versus intermittent PT infusions. Although not definitive with respect to extended-infusion dosing, the findings provide support for improved clinical outcomes with optimizing dosing strategies of our existing antibacterial agents to maximize fT > MIC. A common concern when considering continuous or extended-infusion regimens in children is that compatibility issues could arise due to the child's limited number of intravenous (IV) access

sites, although this is less problematic with extended-infusion regimens compared with continuous infusion regimens.

After conducting a PubMed search using combinations of the terms *piperacillin/tazobactam, beta-lactam, pharmacodynamics, pharmacokinetics, prolonged infusion*, and *extended infusion*, it was determined that description of EIPT in a pediatric population is limited to 1 study which explored the probability of pharmacodynamic target attainment using Monte Carlo simulations and no direct patient intervention. [27] By simulating an extended or continuous infusion of β-lactam antibacterial agents, the authors reported an increased probability of target attainment for *Pseudomonas aeruginosa* isolates with elevated MICs. Although this study is useful for estimating effects of prolonged infusion, an ability to administer medications as prolonged or continuous infusions in actual patients was not addressed. Having implemented an EIPT dosing protocol in our institution, the objective of the current study was to describe implementation of an EIPT dosing strategy as the standard of care in a children's hospital.

Methods

Study Population and Setting

This was a descriptive study performed after the implementation of EIPT as the standard of care in a freestanding, tertiary care children's hospital. At our institution, PT is a common combination antibacterial agent for suspected or confirmed gram-negative bacterial infections. Traditionally, it has been dosed at 75 mg/kg/dose (based on piperacillin component) every 6 to 8 hours via a 30-minute infusion. In April 2011, our health system's Pharmacy and Therapeutics Committee, with the support of the Pediatric Antimicrobial Stewardship Program (PAS), approved a system-wide change to 4-hour infusions of PT. Based on our institutional susceptibility data, it was estimated that the target $fT > MIC$ would be achieved in 15% to 30% more isolates of *P aeruginosa* with EIPT. This was a system-wide change in dosing strategy for both pediatric and adult patients in each of the system hospitals, with PAS support. After hospital-wide education to pharmacists, physicians, and nurses provided by PAS members and the nursing education team, our hospital changed its traditional practice to dosing PT at 100 mg/kg/dose (based on piperacillin component) every 8 hours via 4-hour infusion. This regimen became the standard PT dose and administration method for all patients in the hospital with the exception of neonates or patients encountered in the neonatal intensive care unit, operating areas, outpatient infusion clinics, or emergency department. Although published pediatric pharmacodynamic simulations used a 3-hour infusion time, our hospital is part of a larger health care system consisting of both adult and adult/pediatric mixed hospitals, and a 4-hour infusion time was chosen for system standardization as well as smart pump programming. [27]

Prescribers within our institution are required to order IV antibacterial agents via a preprinted order form. Implementation of the new dosing strategy included changing the dosing on the required preprinted form to the extended-infusion regimen and removing the traditional 30-minute infusion. Prescribers were allowed to order PT via a 30-minute infusion if they thought that dosing was medically necessary, but prescribers had to write the entire medication order, including dose, on a blank line on the order form. Both the 4-hour and 30-minute infusions were administered by using an Alaris Pump (CareFusion Corporation, San Diego, California).

Patients were included if they received at least 1 dose of IV PT within our institution from April 5, 2011, to July 5, 2011, which was a period after EIPT implementation. Patients were identified daily by using the pharmacy computer system and by reviewing inpatient antibacterial orders. Exclusion criteria were admission to the neonatal intensive care unit, age <30 days, and PT administration in the operating areas, outpatient infusion clinics, or emergency department. These exclusions were the same as are listed in the hospital's EIPT dosing protocol. The institutional review board at Indiana University–Purdue University at Indianapolis approved the study with waiver of consent.

Data were collected prospectively from the patient's medical record as a quality assurance project relating to the relationship of PAS and the Quality Council at our institution. Subsequently, exempt institutional review board approval was granted on the decision to share our experience. Patient demographic characteristics were collected in addition to PT dosing information (dose, frequency, infusion time, and duration of therapy), concomitantly ordered medications, number of available IV lumens, and indication for PT. Medications and IV access points were documented once at the time of data collection, although these parameters may have been frequently changing. Therapy was defined as targeted if a specific infection was targeted (cystic fibrosis exacerbation, positive culture, perforated appendicitis, and hospital-acquired pneumonia) or empiric if PT was administered for febrile neutropenia or in the process of ruling out an infection. Reasons for not using the 4-hour infusion time were obtained as documented in the medical record; pharmacists or physicians were queried for this information if it was not found in the medical record. At the end of the study period, the institutional IV placement team was questioned regarding an observed change in peripheral IV placement. The primary outcome in this study was the feasibility of EIPT, determined by the percentage of PT courses that were changed to the traditional 30-minute infusion. A low percentage (<20%) of use of traditional infusions would confirm feasibility of this dosing strategy.

Statistical Analysis

Descriptive statistics were used for patient demographic characteristics, the percentage of PT courses administered via extended infusion, and the percentage of dosing errors. Statistical analysis was conducted by using Microsoft Excel 2007 (Microsoft Corporation, Redmond, Washington).

Results

A total of 332 patients met study inclusion. Median patient age was 5 years (interquartile range, 1.9–12 years), and median weight was 19.9 kg (interquartile range, 11.7–37.6 kg). Age distribution is described in **Table I**. The pediatric critical care, hematology/oncology, general surgery, and pulmonary services were responsible for prescribing 65.1% (n = 216) of PT courses. Approximately 45% of patients received PT as empiric therapy while awaiting culture results ("rule outs") or for febrile neutropenia (**Table II**). The mean duration of PT therapy was 4.5 (4.2) days, with 51.2% (n = 170) of courses lasting <72 hours. Sixty-four (19.3%) courses of PT continued for >7 days. Courses of duration >72 hours but <7 days likely represent antibiotic de-escalation based on culture and susceptibility results or diagnostic indecision. A total of 174

(52.4%) patients had only 1 IV access point at time of PT initiation, and 107 (32.3%) had only 2 IV access points; 149 (44.9%) patients had only peripheral access.

Table I.	
Demographic characteristics (N = 332).	
Male	50.60%
Median age (IQR), y	5 (1.9-12)
Age, no. (%)	
<1 y	55 (16.6)
1-5y	118 (35.5)
6-11 y	67 (20.2)
12-17 y	58 (17.5)
≥18 y	34 (10.2)
Prescribing pediatric medical service, no. (%)	
Burn	1 (0.3)
Cardiology/cardiovascular surgery	23 (6.9)
Critical care	67 (20.2)
Developmental	17 (5.1)
Gastroenterology	10 (3.0)
General surgery	39 (11.7)
Genitourinary	11 (3.3)
Hematology/oncology	75 (22.6)
Hospitalist	6 (1.8)
Infectious diseases	3 (0.9)
Nephrology	4 (1.2)
Neurosurgery	4 (1.2)
Orthopedics	4 (1.2)
Plastic surgery	9 (2.7)
Pulmonary	35 (10.5)
Transplant	13 (3.9)
Trauma	3 (0.9)
Stem cell transplant	8 (2.4)

Table II.	
Indications for piperacillin/tazobactam prescription (N = 332).	
Indication	No. (%) of
Abdominal infection	32 (9.6)
Community-acquired pneumonia	20 (6.0)
Cystic fibrosis	18 (5.4)
Febrile neutropenia	58 (17.5)
Hospital-/health care-/ventilator-associated pneumonia	20 (6.0)
Directed therapy (blood or urine culture)	25 (7.5)
Rule-out infection	92 (27.7)
Tracheitis	13 (3.9)
Urinary tract infection (empiric)	7 (2.1)
Other	47 (14.2)

Twenty-eight (8.5%) of the 332 study patients who qualified for EIPT according to hospital protocol were given traditional dosing and infusion times. Nineteen of those patients (5.7% of all patients) were originally prescribed EIPT and were subsequently changed to traditional dosing during therapy. Documented reasons for using a 30-minute infusion are shown in **Table III**.

Table III.	
Documented reasons for 30-minute piperacillin-tazobactam infusion (n = 28).	
Reason	No. (%) of Patients
Incompatibility with vancomycin coadministration	17 (60.7%)
Incompatibility with other IV medications	5 (17.9%)
Concern for limited IV access	2 (7.1%)
Prescriber confusion	2 (7.1%)
Dosing adjustment in acute kidney injury	1 (3.6%)
Organ procurement protocol	1 (3.6%)

Dosing errors occurred in a low percentage of patients who received PT (n = 6 [1.8%]). Five patients were given doses lower than intended for EIPT. Two of these patients were prescribed doses more similar to the traditional dosing (75 mg/kg every 6 hours). Three errors occurred when patients received 90 mg/kg instead of 100 mg/kg as an extended infusion. In 1 case, a prescriber ordered standard traditional dosing regimen, and that dose was lower than typically used at our institution (65 mg/kg every 6 hours). Four nondosing medication errors were reported. Precipitation occurred in 1 case when vancomycin was administered shortly after PT, although the catheter was flushed with 20 mL of D5 $\frac{1}{2}$NS with 10 mEq of KCl per liter (the patient's maintenance fluid) after PT administration and before vancomycin administration. Doses were infused over an incorrect time period twice; in 1 case, a 4-hour infusion was given over 30 minutes and in the other case, a 30-minute infusion was given over 4 hours. The final error occurred when an EIPT milligram dose was changed, but the order was entered to be administered over and was given over 30 minutes rather than 4 hours. In cases of incorrect infusion time, no patient experienced an adverse effect.

Discussion

One advantage of the extended-infusion dosing strategy is the improvement in the probability of target attainment for microorganisms with higher MICs.[27] Critics may argue that the number of organisms with elevated MICs is lower in the pediatric population compared with the adult population. Although it may be true that children are less likely to be infected with resistant organisms compared with adults, higher MICs are certainly observed for organisms infecting children.[3, 6 and 27] Furthermore, optimizing dosing on the basis of pharmacodynamic parameters may delay development of further resistance in this population, suggesting that such strategies may be particularly effective when introduced before observation of elevated MICs.[10]

Another potential advantage is the economic benefit of the extended infusion strategy. In adults, lower daily doses administered by using extended infusion achieve comparable pharmacodynamic exposures to higher daily dosing regimens administered by intermittent infusion.[16] The omission of 1 daily dose can lead to cost savings although this is of uncertain benefit in children, in whom the medication cost per dose is lower than in adults. However, preparation and administration of 3 doses daily versus 4 doses (the resulting difference with EIPT compared with traditional dosing in our institution), are associated with a decrease in pharmacy preparation and nurse administration time costs. These costs are more difficult to quantify than medication acquisition costs, but they are equally important. In addition, reducing the daily number of IV line accesses may be a beneficial infection control consideration. By limiting possible complications such as catheter-associated bloodstream infections and associated effects on length of stay, by potentially decreasing infections with multidrug-resistant organisms, and by optimizing outcomes, cost benefits may be substantial with this dosing strategy.

Extended-infusion PT regimens were successfully implemented as the standard of care at our freestanding children's hospital. Ninety-two percent of patients received extended infusion dosing of PT. Only 8.4% of PT courses that could have been dosed by extended infusion were dosed using the traditional 30-minute infusion. Of the courses administered over 30 minutes, 86% (24 of 28) were due to incompatibility issues or practitioner concerns.

A preprinted order form is required for ordering IV antibiotics at our institution. When the dosing on the order form was changed to reflect EIPT (every 8-hour dosing administered over 4 hours), there were concerns raised that prescribers desiring an every 6-hour dosing regimen would be more likely to choose a dose that was inappropriate. Since implementation of EIPT, the incidence of dosing errors has been low. However, there are no "baseline" data with which to compare this, and errors are voluntarily reported. The few observed dosing errors were likely attributable to the overall ordering process at our institution, which requires ordering as the milligram per kilogram dose as total PT rather than based on piperacillin component as is commonly documented in pediatric dosing references. We suspect that the dosing errors were more likely due to the overall ordering process than to a change in dosing protocol.

A fewer number of IV access points in combination with a sometimes large number of necessary IV medications, with or without compatibility information, may be more of a challenge in a small child compared with a larger adult. Limited IV access resulting in compatibility concerns

was the indication for reversion to the traditional dosing in 86% of occurrences, but the overall incidence of reversion to traditional dosing from EIPT due to this reason was 7%.

Another barrier suggested before EIPT implementation was that, to comply with the dosing strategy, there would be an increased placement of IV catheters in the pediatric patients. Indeed, addition of more IV access sites to accommodate this dosing strategy is a concern given the increased risk of infection of new IV access sites, which is why this practice was discouraged at our institution. Although prescribers were instructed to change dosing instead of adding additional IV access, it is possible that IV access did increase. Unfortunately, this study did not include comparing patients receiving extended infusion with patients receiving traditional infusion. However, the "IV team" at the institution, which is responsible for obtaining peripheral IV access in patients with difficult-to-obtain IV access, observed no increased requests for peripheral IV insertion after implementation of EIPT. It was also shown that central access was not necessary for use of this dosing regimen, as 45% of patients had only peripheral access at the time of antibiotic initiation.

The largest observed barrier to administration of EIPT was the lack of medication compatibility information, especially with vancomycin. Compatibility data for the concentrations of PT and vancomycin used at our institution (112.5 mg/mL of PT and 10 mg/mL of vancomycin) are not available, and compatibility for other concentrations is reported to be variable.[28]

There are limitations to the current study. It may be difficult to generalize our findings and experience to other hospitals or units providing medical care to children because our institution is a tertiary care pediatric hospital with an overall institutional support structure, in both personnel and technological resources, for this type of dosing change. Administration issues and medication variances may have been present and either escaped identification or documentation during the implementation. However, it is unlikely that a large number of unidentified errors or problems occurred without drawing the attention of the prescribers or the nursing staff who were highly invested in the dosing change. Our study period immediately followed EIPT implementation, and it is not evident if our immediate findings will be continued. However, we have no evidence to suggest that our success will not be sustainable.

Conclusions

Results of this study suggest that extended-infusion PT dosing was feasible in this specific children's hospital. A high percentage of patients (92%) received our institution's preferred dosing regimen; a small percentage of patients still needed to receive traditional infusion times. Additional studies are warranted to determine the impact of this new dosing regimen on clinical outcomes and prevalence of bacterial resistance.

REFERENCES

1. Qin X, Zerr DM, Weissman SJ, et al. Prevalence and mechanisms of broad-spectrum beta-lactam resistance in Enterobacteriaceae: a children's hospital experience. Antimicrob Agents Chemother. 2008;52:3909–3914.

2. El-Mahallawy HA, El-Wakil M, Moneer MM, Shalaby L. Antibiotic resistance is associated with longer bacteremic episodes and worse outcome in febrile neutropenic children with cancer. Pediatr Blood Cancer. 2011;57:283–288.

3. Wisplinghoff H, Seifert H, Tallent SM, et al. Nosocomial bloodstream infections in pediatric patients in United States hospitals: epidemiology, clinical features and susceptibilities. Pediatr Infect Dis J. 2003;22:686– 691.

4. Krontal S, Leibovitz E, Greenwald-Maimon M, et al. Klebsiella bacteremia in children in southern Israel (1988 –1997). Infection. 2002;30:125–131.

5. Raymond J, Aujard Y. Nosocomial infections in pediatric patients: a European, multicenter prospective study. European Study Group. Infect Control Hosp Epidemiol. 2000;21:260 –263.

6. Lee CY, Chen PY, Huang FL, Lin CF. Microbiologic spectrum and susceptibility pattern of clinical isolates from the pediatric intensive care unit in a single medical center— 6 years' experience. J Microbiol Immunol Infect. 2009;42:160–165.

7. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Develop-
mental pharmacology— drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349:1157–11567.

8. Foglia EE, Fraser VJ, Elward AM. Effect of nosocomial infections due to antibiotic resistant organisms on length of stay and mortality in the pediatric intensive care unit. Infect Control Hosp Epidemiol. 2007;28:299–306.

9. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. ClinInfectDis.1998;26:1–10.

10. Rybak MJ. Pharmacodynamics: relation to antimicrobial resistance. Am J Med. 2006;119:S37–S44.

11. Kim A, Kuti JL, Nicolau DP. Probability of pharmacodynamic target attainment with standard and prolonged infusion antibiotic regimens for empiric therapy in adults with hospital-acquired pneumonia. Clin Ther. 2009;31: 2765–2778.