Original Article

Administration of Extended Infusion Piperacillin-Tazobactam With the Use of Smart Pump Technology

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Abstract

Background: For beta-lactams, the parameter that best predicts bacterial killing is the length of time the antibiotic concentration exceeds the minimum inhibitory concentration (MIC). Studies have demonstrated improved outcomes with extended infusion (4-hour) piperacillin-tazobactam (P-TZ) compared with traditional immediate infusions.

Objectives: To describe how one institution made the conversion from immediate infusion of P-TZ to a 4-hour extended infusion utilizing an approved automatic therapeutic substitution, staff education, and smart pump technology, and to examine the impact of this conversion on patient length of stay and pharmacy costs.

Methods: With approval from the Pharmacy and Therapeutics (P&T), Antimicrobial Stewardship, and Medical Executive Committees, the decision was made to automatically convert all P-TZ orders to a standardized 4-hour infusion given every 8 to 12 hours depending on renal function. The medical records of all adult patients receiving P-TZ during 12 months pre implementation and 24 months post implementation of a 4-hour extended infusion of P-TZ were retrospectively analyzed for length of stay and mortality. The cost of P-TZ was also assessed during these time periods.

Results: With the help of smart pump technology, our institution successfully completed a conversion to 4-hour extended infusion P-TZ. Through this conversion, pharmacy expenditure of P-TZ was reduced by 38%; the total cost savings was \$387,980.62 for the 24-month postintervention phase. Extended infusion P-TZ reduced hospital length of stay by 0.6 days ($P < .05$), resulting in an additional cost savings of \$1,689,480 for the 24-month postintervention phase. A conservative estimate of total cost savings to the hospital in the first 24 months, including the reduction in P-TZ expenditures, was \$2,077,460.

Key Words—antibiotics, length of stay, piperacillin-tazobactam, smart pump technology

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Infections caused by antibiotic-resistant bacteria are a great concern to public health, as growing resistance among both gram-positive and gram-negative pathogens is observed.¹ Data from the Centers for Disease Control and Prevention (CDC) show rapidly rising rates of infection due to methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), and

fluoroquinolone-resistant *Pseudomonas aeruginosa*.² Even more concerning is the fact that the number of new antibacterial drugs approved for marketing in the United States is dramatically decreasing.³

The increase in resistance of organisms and the availability of fewer effective antibiotics have led infectious disease specialists to reevaluate optimal methods of administering intravenous (IV) antibiotics.^{4,5}

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The relationship between the pharmacokinetics and pharmacodynamic activity of beta-lactam antibiotics influences their dose and effectiveness in eradicating pathogens, and the time above the minimum inhibitory concentration (MIC) is an important marker for efficacy.⁶⁻¹⁰ Studies have shown that bactericidal effects of penicillins are maximized when the drug concentrations are higher than the MIC for greater than 50% of the dosing interval.¹¹

PIPERACILLIN-TAZOBACTAM

Sustaining bactericidal serum drug concentrations greater than the MIC is more likely when piperacillin-tazobactam (P-TZ) is administered as an extended infusion. This was demonstrated by Lodise and colleagues in a retrospective review comparing 4-hour extended infusion P-TZ versus 30-minute infusion of P-TZ in patients with documented *P. aeruginosa* infections.¹² Their landmark study showed a greater than 50% decrease in 14-day mortality and a 17-day decrease in hospital length of stay (LOS) in those patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 17 or higher; however, overall mortality benefit in patients with APACHE II scores less than 17 were not seen in the study.¹²

In the Retrospective Cohort of Extended-Infusion P-TZ (RECEIPT) study, the effectiveness of extended-infusion P-TZ was compared with that of similar spectrum, nonextended infusion beta-lactam antibiotics in the treatment of documented gram-negative infections.⁴ Antibiotic duration, hospital LOS, and intensive care unit LOS were similar between groups, although in-hospital mortality was significantly decreased in the extended infusion P-TZ group. In a population pharmacokinetic study of extended infusion P-TZ in hospitalized patients with nosocomial infections, investigators concluded that extended infusion of P-TZ was the most effective method of administration for patients with nosocomial infections.¹³

Not all studies reported significant benefit from extended infusion administration of P-TZ.^{14,15} A multisite, retrospective cohort study compared extended

infusion with nonextended infusion of P-TZ. No impact was noted on 30-day mortality or LOS overall or in any of the subgroups studied.¹⁴ Most recently, a single-center trial concluded that prolonged infusion offered no advantage over intermittent infusion antibiotic therapy, however extended infusion of P-TZ was limited to 3 hours and 54 patients.¹⁵

HOSPITAL CASE STUDY

Sanford Health is an integrated health system headquartered in Sioux Falls, South Dakota, and Fargo, North Dakota. Sanford is the largest, rural, not-for-profit health care system in the nation with locations in 126 communities in 8 states. Sanford Health includes 35 hospitals, 140 clinic locations, and more than 1,300 physicians in 81 specialty areas of medicine.¹⁶ The data for this case study are from Sanford USD Medical Center, a 478-bed general medical and surgical teaching hospital in Sioux Falls. The hospital had 23,886 admissions in the latest year for which data are available and performed 9,636 annual inpatient and 27,351 outpatient surgeries.

As discussed previously, studies have demonstrated that infusing P-TZ over 4 hours can lead to optimization of antimicrobial efficacy. With approval from the P&T Committee, the decision was made to automatically convert all P-TZ orders to a standardized 4-hour infusion given every 8 to 12 hours (depending on renal function [Table 1]) in the adult inpatient population. The therapeutic interchange was also approved by the Antimicrobial Stewardship and Medical Executive Committees and was implemented in March 2010.

Ensuring that involved staff are appropriately educated is a vital factor for success when implementing any new program. Pharmacists were educated in regard to the new approved therapeutic interchange, changes in workflow, and rationale at staff meetings. Nurses were educated on the change by pharmacists at nursing unit huddles and nursing senate. Physicians were sent a letter to inform them of the change. In addition, there was an analysis of the impact on the number of pumps needed and implications to the patients.

Table 1. Automatic conversion P-TZ dosing

Renal function	P-TZ dose
CrCl ≥ 20 or on CRRT	3.375g IV q8h infused over 4 hours
CrCl < 20 or on peritoneal dialysis or hemodialysis	3.375g IV q12h infused over 4 hours

Note: CRRT = continuous renal replacement therapy; IV = intravenous; P-TZ = piperacillin-tazobactam; q8h = every 8 hours; q12h = every 12 hours.

In addition to staff education, an important component of changing practice habits is utilizing new technologies when available. For many reasons, such as inability to dedicate an IV line to infusion of P-TZ and resultant incompatibilities, nursing is often reluctant to infuse over the entire 4 hours. The 4-hour infusion of all P-TZ orders was possible at Sanford USD Medical Center, because a successful smart pump infusion system (Hospira, Lake Forest, IL) had already been installed. The advanced infusion pump technology has a unique combination of nurse-friendly features, auto-default to safety software, and extensive configurability for flexibility. The smart pump infusion system features were utilized for this conversion by creating a specific 4-hour P-TZ library entry to create a forced function by utilizing hard limits to ensure a 4-hour infusion duration. When the new process was implemented, nursing was educated on the new specific 4-hour P-TZ library entry and stickers were placed on the P-TZ IV bags as an additional reminder of the new smart pump entry. Smart pump technology assists with process implementation and creates an opportunity to change practice and culture.

RESULTS

Random audits and “just in time” training were conducted on nursing units to ensure compliance with the 4-hour extended infusion practice on P-TZ for smart pump programming and on the pharmacy side for correct infusion duration in the electronic medical record. The audit results of pharmacy entry

of P-TZ with 4-hour infusion revealed 100% compliance; nursing selection of the specific 4-hour P-TZ entry in the smart pump library was 91% (Table 2).

The smart infusion pump technology creates a forced function by utilizing hard limits to ensure a 4-hour infusion duration if the specific 4-hour P-TZ smart pump entry is used. In addition, this technology generates data showing how often the nurse inputs an incorrect infusion duration time and is stopped by the hard limit. In the case of extended infusion P-TZ, 38,080 were administered over the 2-year postimplementation period, and the upper hard limit averted an incorrect infusion duration 1,098 times. Of these 1,098 attempts to program the infusion of P-TZ, 53% of them were programmed to infuse at 150% the rate of the upper hard limit, further demonstrating the need for the limits in the smart pump to ensure standard infusion rates are utilized. Over time, there was no trend observed regarding the quantity or severity of attempts to reprogram the infusion time.

Length of Stay and Mortality

During the first 24 months post implementation of 4-hour extended dosing P-TZ, 2,888 patients received P-TZ at our institution. When these data were compared to the 12 months of P-TZ data prior to the conversion, extended infusion P-TZ reduced the average hospital LOS by 0.6 days ($P = .048$) and mortality by 0.7% ($P = .479$) (Table 3). Determination of patient demographic confounders was beyond the scope of this report and not accounted for during statistical analysis.

Table 2. Compliance with P-TZ extended infusion administration

Criteria	June 2011	August 2011
P-TZ 4-hour infusion selected from drug library	42/46 (91%)	42/46 (91%)
P-TZ entered in chart with 4-hour infusion	56/56 (100%)	65/65 (100%)

Note: P-TZ = piperacillin-tazobactam.

Table 3. P-TZ immediate infusion versus 4-hour extended infusion

Infusion	N	Average LOS (days) for all patients	Mortality, n (%)
Immediate infusion (3/1/2009-2/28/2010)	1,367	10.24	122 (8.9%)
4-hour infusion (4/1/2010-3/31/2012) ^a	2,888	9.64	238 (8.2%)
Difference		0.6	0.7%
Significance		$P < .05$	$P > .05$

Note: LOS = length of stay; P-TZ = piperacillin-tazobactam.

^a Study time excluded March 2010 due to use of discharge dates to exclude patient LOS that overlapped pre and post interventions phases.

Cost Savings

In addition to the decreased LOS, an automatic therapeutic interchange of P-TZ 3.375 g every 8 hours (4-hour infusion) would result in a cost avoidance due to decreased total purchasing of P-TZ. Our initial goal of decreasing pharmacy expenditure by 25% one year after implementation of 4-hour extended infusion P-TZ was exceeded with a 38% reduction the first year. The total cost savings was \$387,980.62 for the 24-month intervention phase (**Figure 1**). It is important to note that the number of patients in the 3 years of the study was consistent and that the decrease in P-TZ dollars was not due to a shift to an alternate antibiotic to avoid extended infusion. Based on the data that extended dosing P-TZ reduced hospital LOS by 0.6 days, this would result in additional cost savings of more than \$1,689,480 in 24 months. The cost used to determine this savings is the direct cost (fixed and variable) for the last full day of hospital stay based on fiscal year 2011 data, which was \$975 per day (\$585 per 0.6 day). A conservative estimate of the cost savings to the hospital in the first 24 months, including reduction in P-TZ expenditures, was \$2,077,460.

DISCUSSION

Extended infusion dosing strategies are beneficial, because they allow maintenance of antibiotic concentrations above the MIC of organisms for greater portions of the dosing interval. Studies published in the medical literature support the concept that extending the infusion time of P-TZ to 4 hours maximizes the

pharmacodynamic activity. By using smart infusion pump technology, a function is created that utilizes hard limits to ensure a 4-hour infusion duration, if the specific 4-hour P-TZ smart pump entry is used. Also, this technology generates data that provide information on how often the nurse inputs an incorrect infusion time and is stopped by a hard limit alert. This assists us in pinpointing areas for educational efforts.

Although the smart pump ensured the 4-hour infusion, there were several challenges inherent to the change in IV administration procedure. The number of concurrent IV medication sites along with medication incompatibilities were of concern, and some patients required additional peripheral line placement. Additional pumps or pumps with dual channels were needed, because IV maintenance fluids could not be interrupted for 12 hours a day during these extended infusions. The cost of the additional pumps and lines was minimal. Previous studies were able to show a decreased LOS in critically ill patients with documented *P. aeruginosa* cultures.¹² Our institution observed a statistical significant decrease in LOS when comparing 24 months of extended infusion P-TZ data to 12 months immediate infusion P-TZ patient data. These data included all adult patients receiving P-TZ, regardless of indication, severity, or culture results.

In our experience, implementation of extended infusion P-TZ decreased hospital stay by 0.6 days resulting in cost savings of \$1,689,480 for the 24-month postintervention phase. The goal of

Figure 1. Annual costs of piperacillin-tazobactam in a hospital setting: Pre and post implementation of a 4-hour extended infusion use policy.

decreasing pharmacy expenditure by 25% one year after implementation of 4-hour extended infusion P-TZ was exceeded with a 38% reduction. The total drug cost avoidance was \$387,980.62 for the 24-month postintervention phase. Total estimate of cost savings to the hospital in the first 24 months exceeded 2 million dollars.

This experience with P-TZ extended infusion resulted in a smooth transition to other extended infusion antibiotics, such as doripenem, within our hospital. The relationship between the pharmacokinetics and pharmacodynamic activity of beta-lactam antibiotics influences their dose and effectiveness in eradicating pathogens, where the time above the MIC may be an important marker for the efficacy of carbapenems, including doripenem.

CONCLUSION

We studied the impact of implementing an automatic therapeutic interchange of P-TZ 3.375 g every 8 hours using an extended 4-hour infusion rate. By using smart pump technology, we were able to change habits and ensure accuracy of administration of extended infusion P-TZ. Also, this technology made it easier to implement extended infusions with other antibiotics. We realized an approximate cost savings of 2 million dollars over the 24-month postimplementation phase, and patients' LOS was decreased significantly (0.6 days).

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