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Use of Population Pharmacokinetics and Electronic Health Records to Assess Piperacillin-Tazobactam Safety in Infants

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Abstract

Background—Piperacillin, in combination with tazobactam, is frequently used in infants for treating nosocomial infections, although safety data in this population are limited. Electronic health record (EHR) data can be used to evaluate drug safety in infants, but measures of drug exposure are lacking.

Methods—To relate simulated piperacillin exposure with adverse events (AEs) in infants using EHR data, we identified infants discharged from 333 neonatal intensive care units managed by the Pediatrix Medical Group between 1997 and 2012. Using a previously published population PK model in the target population, we simulated piperacillin steady-state area under the concentration vs. time curve from zero to tau ($AUC_{ss,0-\tau}$) and maximal drug concentration ($C_{max,ss}$). Next we used multivariable logistic regression to evaluate the association between simulated $AUC_{ss,0-\tau}$ and

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C_{max,ss} with clinical AEs (seizure and rash) and laboratory AEs controlling for gestational age. The odds ratios (95% confidence intervals) comparing the third vs. the first tertiles for AUC_{ss,0-τ} and C_{max,ss} were reported.

Results—We identified 746 infants with a median (interquartile range) gestational age of 30 weeks (26, 33) and postnatal age of 11 days (6, 25). The median (interquartile range) piperacillin dose was 225 mg/kg/day (176, 300). No significant associations were found between simulated piperacillin exposure (AUC_{ss,0-τ} and C_{max,ss}) and clinical and laboratory AEs.

Conclusions—We found no associations between predicted piperacillin exposures and the occurrence of AEs. This study confirms the feasibility of using population pharmacokinetics and EHR to relate drug exposure with safety.

Keywords

piperacillin; population pharmacokinetics; antibiotics; safety; infants; pediatrics

INTRODUCTION

Piperacillin, in combination with tazobactam, is often used to treat infants with nosocomial infections, such as intra-abdominal infections and neonatal sepsis, because of its broad-spectrum coverage and relative safety in adults. Most adverse events (AEs) observed with use in adults are mild to moderate in severity and the most common events include diarrhea, headache, constipation, nausea, insomnia, and rash.¹ According to one study, piperacillin-tazobactam was the fourth most commonly prescribed antibiotic in the neonatal intensive care unit (NICU), and piperacillin-tazobactam was more likely to be prescribed to premature infants than term infants.² Despite the frequent use of piperacillin-tazobactam in infants, little is known about its safety in this population.³

Evaluating drug safety in infants is challenging for several reasons. Performing trials with an adequate number of infants to assess drug safety requires considerable time and resources. Moreover, the difficulty recruiting participants and low consent rates can make this task even more daunting. An adequate age distribution is required to evaluate drug safety in infants of varying gestational and postnatal ages. Also, some safety events may be rare in infants and can be missed in clinical trials of limited sample size. Using electronic health record (EHR) data from national databases can be a suitable approach to evaluate drug safety in infants since it can overcome many of these limitations of traditional clinical trials.

The national database used in this study contains a large amount of EHR data collected from many infants, which is useful for investigating drug safety and detecting rare events. However, as with most EHR databases, there is frequently no measure of drug exposure. A major challenge with conducting pharmacokinetic (PK) studies in infants is obtaining sufficient blood samples for analysis because of the small size and limited blood volume of infants. There are also federal regulations that restrict the amount of blood volume taken from infants for research purposes.⁴ This constraint can be overcome by applying population PK modeling using sparse blood samples to simulate drug exposure. A recent study confirmed the utility of using EHR data and pharmacokinetic modeling to assess the safety

of ampicillin and seizure risks in neonates.⁵ Although this approach was cost-effective and minimized risk by using simulated PK concentrations and routinely collected safety data, it might not be generalizable so the relationship between exposure and safety must be evaluated for other drugs.

A population-based PK model was recently developed in infants that accounted for the effect of body weight (WT) and postmenstrual age (PMA) on piperacillin clearance (CL).⁶ The goal of this study was to leverage this previously published population PK model to simulate piperacillin exposure in infants using EHR data from a large cohort of infants receiving piperacillin-tazobactam in the NICU, and then relate simulated exposure to AEs of piperacillin-tazobactam in this population.

MATERIALS AND METHODS

Study Design and Data Source

We identified all premature and term infants exposed to piperacillin-tazobactam and discharged from 333 NICUs managed by the Pediatrix Medical Group from 1997–2012. The EHR prospectively captures information including daily progress notes, laboratory results, admission and discharge notes, and maternal information. The study was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without identifiers. We included infants in this study if they received piperacillin-tazobactam and were comparable in age (<61 days postnatal age [PNA] and 25–48 weeks PMA) and weight (<3990 g) to the infants used to develop the PK model.⁶ All infants in this study received the combination product, piperacillin-tazobactam; however, the analyses evaluating the relationship between safety and exposure were only for the piperacillin component.

Exposure Simulations

The published population PK model that was used to simulate piperacillin exposure was based on a one-compartment structural PK model with a proportional plus additive residual error model.⁶ The final model included PMA and WT as covariates for CL, and included WT as a covariate for volume of distribution (V): $CL\text{ (L/h)} = 0.080 \cdot WT \cdot (PMA/33)^{1.76}$ and $V\text{ (L)} = 0.42 \cdot WT$.⁶ Inter-individual variability in CL was 37%, whereas no inter-individual variability was estimated for V. We performed simulations using the software NONMEM (version 7.2, Icon Development Solutions, Ellicott City, MD). We simulated exposure for each infant from the EHR that met our inclusion criteria using their individual PMA, WT, and dosing information. The elimination rate constant (K_E) was calculated using equation 1 and the elimination half-life was calculated using equation 2. We calculated the steady-state area under the concentration vs. time curve from zero to tau ($AUC_{ss,0-\tau}$) using Equation 3, and then calculated the steady-state maximal concentration ($C_{max_{ss}}$) according to Equation 4, where T' is the infusion time and τ is the dosing interval. We reported the predicted $C_{max_{ss}}$, CL, and $AUC_{ss,0-\tau}$ for these infants. Cumulative area under the concentration versus time curve (AUC) was calculated for the entire duration of exposure by multiplying the daily $AUC_{ss,0-\tau}$ by the total days of exposure.

$$K_E = CL/V \quad (1)$$

$$\text{Half-life} = 0.693/K_E \quad (2)$$

$$AUC_{ss,0-\tau} = \frac{Dose}{CL} \quad (3)$$

$$C_{max_{ss}} = \frac{Dose}{CL \cdot T} \cdot \frac{1 - e^{-K_E \cdot T}}{1 - e^{-K_E \cdot \tau}} \quad (4)$$

Definitions

We evaluated the safety of piperacillin-tazobactam by identifying clinical and laboratory AEs recorded in the EHR on a day an infant was exposed to piperacillin-tazobactam. We selected AEs by reviewing the piperacillin-tazobactam United States Food and Drug Administration product label for commonly described clinical and laboratory AEs.¹ We focused on clinical AEs that were reliably recorded and feasible to measure in infants from a retrospective database, which included seizure and rash. We identified the following laboratory AEs: hyponatremia, hypokalemia, elevated creatinine, leukopenia, thrombocytopenia, low hematocrit, prolonged prothrombin time, prolonged thromboplastin time, and elevated aspartate aminotransferase or alanine aminotransferase. The distinction between AEs and serious adverse events (SAEs) for the laboratory events are defined in Table 1.⁷ We reported the proportion of infants experiencing a clinical or laboratory AE while exposed to piperacillin-tazobactam. We assumed that infants did not have a clinical or laboratory AE or SAE if the event was not recorded in the medical chart. We excluded clinical and laboratory events occurring on the first day of piperacillin exposure to ensure that the infants had reached steady state and because we lacked time of day for drug dosing and AEs.

Statistical Analysis

We used standard summary statistics to describe demographic characteristics; continuous variables were presented as median (interquartile range [IQR]) and categorical variables were presented as count (percentages). We used multivariable logistic regression to evaluate the association between $AUC_{ss,0-\tau}$, cumulative AUC, and $C_{max_{ss}}$ with the presence of a clinical or laboratory AE on any day of exposure to piperacillin controlling for gestational age at the infant level. We report odds ratios (95% confidence intervals) comparing the third vs. the first tertiles for $AUC_{ss,0-\tau}$ and $C_{max_{ss}}$. All analyses were performed using Stata 14.0 (StataCorp LLC, College Station, TX).

RESULTS

We identified 746 infants meeting the study inclusion criteria who received 777 courses of piperacillin-tazobactam for a total of 5879 infant days (Table 2). The median gestational age and postnatal age at first drug exposure were 30 weeks (IQR; 26, 33) and 11 days (6, 25), respectively. The median (IQR) birth weight was 1220 g (854, 1789). The median piperacillin dose received was 225 mg/kg/day (176, 300), and median duration of exposure was 11 (8, 14) days. The majority (610 [82%]) of infants received their first dose of piperacillin-tazobactam between 3–29 days of age. Positive blood cultures during treatment were present in 18 infants (2%). Of 673/746 infants with mortality data, 64/673 infants (10%) died prior to hospital discharge.

Simulated Piperacillin Exposure

The median (IQR) simulated weight normalized CL was 0.077 (0.056, 0.100) L/hr/kg, the median (IQR) $C_{max_{ss}}$ was 276 (213, 352) mg/L, and the median (IQR) simulated $AUC_{ss,0-\tau}$ was 1318 (922, 1851) mg*hr/L. The median (IQR) simulated weight normalized V was 0.422 (0.420, 0.423) L/kg. The highest and lowest tertiles for $AUC_{ss,0-\tau}$ were 1658 to 7977 mg*hr/L and 258 to 1040 mg*hr/L, respectively. The highest and lowest tertiles for $C_{max_{ss}}$ were 335 to 930 mg/L and 75 to 238 mg/L, respectively.

Relationship between Safety and Piperacillin Exposure

The incidence of clinical AEs experienced during piperacillin-tazobactam treatment were seizures in 10 infants (1.3%) and rash in 6 infants (0.8%). The most common laboratory AEs were low hematocrit in 263 infants (35%) and thrombocytopenia in 242 infants (32%) (Table 1). There was no statistically significant associations between clinical or laboratory AEs with simulated $AUC_{ss,0-\tau}$ or $C_{max_{ss}}$ (Table 3). There were also no statistically significant associations between laboratory SAEs with simulated $AUC_{ss,0-\tau}$ or $C_{max_{ss}}$ for those laboratory SAEs with sufficient sample sizes for multivariable model convergence. We also evaluated the association between AEs and cumulative AUC, and similar findings were observed (data not presented). The adjusted odds ratios (95% CI) for laboratory SAEs and simulated $AUC_{ss,0-\tau}$ were 0.24 (0.03, 2.20) for hypokalemia, 1.08 (0.60, 1.94) for thrombocytopenia, 0.21 (0.02, 1.84) for leukopenia, and 0.72 (0.37, 1.40) for low hematocrit. The adjusted odds for any SAE in complete blood cell count results and simulated $AUC_{ss,0-\tau}$ were 1.01 (0.65, 1.56). The adjusted odds ratios (95% CI) for laboratory SAEs and simulated $C_{max_{ss}}$ were 0.29 (0.03, 2.59) for hypokalemia, 1.17 (0.62, 2.22) for thrombocytopenia, 0.21 (0.02, 1.85) for leukopenia, and 0.79 (0.40, 1.53) for low hematocrit. The adjusted odds for any SAE in complete blood cell count results and $C_{max_{ss}}$ were 1.31 (0.90, 1.92).

DISCUSSION

We present the largest retrospective safety study of piperacillin-tazobactam therapy conducted in infants to date and found no association between piperacillin exposure and AEs. The incidences of seizures and rash observed in these infants were low (1.3% and 0.8%) and were similar to those observed in adults (<1% and 4.2%, respectively) during

clinical trials.¹ The incidence of elevated creatinine was 2% in this study vs. 1.8% in adults and elevated aspartate aminotransferase and alanine aminotransferase were 1% and 0.5% in this study compared to 1.4% for adults.¹ The incidences of some laboratory AEs were higher in infants in this study compared to those reported in adults during clinical trials: hyponatremia (2% vs. <1%), hypokalemia (6% vs. <1%), leukopenia (12% vs. <1%), and thrombocytopenia (32% vs. <1%).¹ This discrepancy in the incidences of laboratory AEs between adults and infants could be due in part to difference in the underlying disease condition, concomitant medications, or criteria for determining normal laboratory values among different age groups.

In this study, piperacillin-tazobactam had a favorable safety profile in infants. This is consistent with previous studies evaluating the safety of piperacillin-tazobactam in infants,^{8,9} however only a few studies have been performed and they have small sample sizes. One prospective study reported that 27 preterm infants given piperacillin-tazobactam did not experience any clinically related AEs or clinically relevant changes in laboratory parameters.⁸ A separate retrospective study in 252 newborns evaluated the safety and efficacy of piperacillin-tazobactam in neonates found no drug-related SAEs or abnormal renal or gastrointestinal symptoms, although one infant developed a rash.⁹ No infants experienced significant changes in white blood counts, platelets, creatinine levels, or liver enzymes, but thrombocytopenia occurred in 35% of infants that received piperacillin-tazobactam for 5–14 days.⁹

The simulated piperacillin PK parameters in this study were similar to the parameter estimates from the study used to generate the simulations.⁶ However, the median weight normalized CL in our study (0.077 L/hr/kg) was approximately half of that from another published population PK study developed in infants less than 2 months of age (0.133 L/hr/kg).¹⁰ This may be due to the younger median (range) gestational age of infants in our study compared to the published study: 29 (23–40) weeks vs. 36 (26–41) weeks.¹⁰ Infants with younger gestational age are expected to have a lower renal CL since the kidneys are less mature. The $AUC_{ss,0-\tau}$ in this study was higher than the AUC from 0 to infinity (296–820 mg*hr/L) reported in 28 neonates (Gestational Age 29–40 weeks) given a single 75 mg/kg dose of piperacillin.¹¹ This might be because the neonates in the published study had higher CL values (0.101–0.145 L/hr/kg) and received a lower dose (75 mg/kg) compared to the median (range) dose of 100 (45–200) mg/kg/dose in our study.¹¹ Similarly, the $AUC_{ss,0-\tau}$ in this study was also higher than the mean (range) model estimated $AUC_{ss,0-\tau}$ [487 (270–700) mg*hr/L] in 12 children whom received 100 mg/kg of piperacillin every 8 hours infused over 4 hours.¹² However, these children were older [median (IQR) age of 5 years (1.75, 6.5)], had higher CL values [mean (range) of 0.22 L/hr/kg (0.14–0.37)], and were critically ill.¹²

We did not observe any statistically significant associations between piperacillin simulated exposure ($AUC_{ss,0-\tau}$ or $C_{max,ss}$) and clinical and laboratory AEs in this cohort of infants. This observation is consistent with other studies evaluating the safety of high dose piperacillin in children and adults.^{13,14} There were no AEs associated with single-dose piperacillin-tazobactam administration in children (2 months–12 years of age) randomized to receive low-dose (50 mg/kg) or high-dose (100 mg/kg) piperacillin.¹³ In addition, high-

dose extended interval piperacillin (6.0 g and 8.0 g of piperacillin every 12 hours) administration was safe and well tolerated in 10 adults with only mild phlebitis (one subject) and mild diarrhea (one subject) observed.¹⁴ However, it is possible that the AEs that we evaluated in this study were not associated with exposure or the doses in this study were not high enough to cause AEs. Although the majority of drug reactions are related to the pharmacology and dose of the drug, some drug reactions are idiosyncratic (such as penicillin-induced anaphylaxis) and are caused by immunological and pharmacogenetics-related mechanisms.¹⁵ Susceptibility to AEs is influenced by many other factors, such as disease states, genetics, gender, and drug interactions, which further complicates this type of analysis.¹⁵ Our study was also performed in infants with normal renal function, and so patients with renal dysfunction might have a different safety profile.

A publication evaluating the safety of ampicillin in neonates using EHR data found that higher ampicillin exposure (AUC from 0 to 24 hours and $C_{max_{ss}}$) but not dosing was associated with an increased odds of seizures.⁵ In particular, a daily $C_{max_{ss}} > 140 \mu\text{g/mL}$ was associated with a 1.76 fold increased odds of seizures (95% CI 1.35, 2.30).⁵ The authors noted that the prevalence of seizure was lower on days when infants received optimal dosing, per recommendations from another published study¹⁶, compared to days when infants received higher or lower dosing.⁵ We did not observe a statistically significant relationship between piperacillin exposure and seizures, which could be due in part to the much smaller sample size in this study (746) compared to the published study (131,723 infants).⁵ Also, the median age of first exposure was only 1 day for ampicillin (compared to 10.5 days for piperacillin-tazobactam) and serum creatinine measurements are considered less reliable in the first few days of life.^{5,17} Alternatively, piperacillin could be less likely to cause seizures than ampicillin because of slight differences in chemical structure and central nervous system penetration. Ampicillin achieves good central nervous system penetration in children with concentrations in the cerebral spinal fluid ranging from 1.6 to 39% to those in blood, whereas the penetration of piperacillin into the central nervous system is considered erratic and highly variable in children with cerebral spinal fluid concentrations ranging from undetectable to 8% to those in blood.¹⁸

Although this approach which merges population PK modeling and EHR data is useful, it has some inherent limitations. One possible concern is that the PK data generated in this study was based on simulations rather than observed drug concentration data. However, consistency of PK parameter estimates with literature values suggests that these simulations are reasonable estimates of drug exposure.^{6,10–12} Also, as an observational study, identification of clinical AEs was restricted to records documented by clinicians, and laboratory AEs were affected by the frequency of laboratory draws. We also assumed that missing clinical or laboratory AEs were normal if they were not recorded in the medical chart. Another limitation is that we could not assess other common AEs observed in children since abdominal pain and constipation¹ are not reliably recorded in the EHR database for infants. In addition, we excluded AEs that occurred on the first day of drug exposure so there is a potential concern that some early-onset AEs were missed. Also, since the exposure rates dictate the sample size, some rare events might not be reliably evaluated with EHR data. However, a post-hoc power calculation revealed that our sample size of 746 was sufficient to identify a 10% prevalence of an adverse event with sufficient precision, defined

as an exact binomial 95% confidence interval within 20% of the mean estimate: 0.1 (0.08, 0.12). Finally, this was a short-term safety analysis, so the long-term safety of piperacillin-tazobactam, such as the effects on the gut microbiome, should be assessed in future studies.

In this study, piperacillin-tazobactam had a favorable safety profile in infants, and there were no significant associations found between simulated piperacillin exposure and safety. Additional prospective studies should be conducted to confirm the safety profile of piperacillin-tazobactam in infants because rare events and common gastrointestinal side effects could not be evaluated in these infants. In conclusion, combining PK modeling with EHR data is a feasible, cost-effective, and novel way to provide a preliminary assessment of drug safety in infants. Ways in which EHR data research might be improved include using EHRs from multiple sites, performing external validation of previously published analyses, and developing approaches to handle missing data.¹⁹

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Table 1

Laboratory Adverse Events and Serious Adverse Events.

Laboratory Event	Adverse Events		Serious Adverse Events	
	AE Values	Infants n=746 (%)	SAE Values	Infants n=746 (%)
Hypnatremia	>155 mmol/L	18 (2)	>160 mmol/L	1 (0.1)
Hypokalemia	<3 mmol/L	43 (6)	<2.5 mmol/L	10 (1)
Elevated creatinine	>1.7 mg/dL	14 (2)	>3.0 mg/dL	0 (0)
Leukopenia	<5000/mm ³	93 (12)	<2000/mm ³	7 (1)
Thrombocytopenia	<100,000/mm ³	242 (32)	<30,000/mm ³	70 (9)
Low hematocrit	<37%	263 (35)	<30%	60 (8)
Prolonged prothrombin time	>15 sec	16 (2)	-	-
Prolonged partial thromboplastin time	>50 sec	9 (1)	-	-
High AST	>600 U/L	7 (1)	>1200 U/L	2 (0.3)
High ALT	>225 U/L	4 (0.5)	>450 U/L	2 (0.3)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase

Table 2

Demographic characteristics of infants exposed to piperacillin-tazobactam.

Demographic Characteristics	N=746,%
Gestational age, weeks	
<26	18%
26–28	26%
29–32	26%
33–36	19%
37	10%
Birth weight, g	
<1000	37%
1000–1499	28%
1500–2499	24%
2500–3499	8%
3500	2%
Age at first exposure, days	
<3	1%
3–6	28%
7–29	53%
30–59	18%
Race/ethnicity	
White	19%
African American	9%
Hispanic	70%
Other	2%
Male	58%
Inborn	74%
Caesarean delivery	66%
Small for gestational age	17%
Died	9%

Table 3

Adjusted odds ratio (95% confidence intervals) for adverse events comparing the third vs. the first tertiles for piperacillin steady-state area under the concentration vs. time curve from zero to tau ($AUC_{ss,0-\tau}$) and steady-state maximal concentration ($C_{max_{ss}}$) controlling for gestational age.

Clinical and Laboratory AEs*	Adjusted Odds Ratio (95% CI) for Third vs. First Tertiles of $AUC_{ss,0-\tau}$ (mg*hr/L)	Adjusted Odds Ratio (95% CI) for Third vs. First Tertiles of $C_{max_{ss}}$ (mg/L)
Seizures	3.63 (0.73, 18.0)	0.75 (0.07, 8.55)
Rash	1.02 (0.14, 7.22)	0.75 (0.12, 4.90)
Hypernatremia	1.24 (0.40, 3.89)	1.01 (0.27, 3.79)
Hypokalemia	0.64 (0.28, 1.42)	0.87 (0.39, 1.98)
Elevated creatinine	0.74 (0.17, 3.20)	0.55 (0.11, 2.81)
Thrombocytopenia	1.24 (0.84, 1.83)	1.10 (0.74, 1.65)
Leukopenia	0.87 (0.51, 1.49)	0.81 (0.46, 1.42)
Low hematocrit	1.11 (0.75, 1.65)	1.14 (0.76, 1.70)
Prolonged PT	0.29 (0.06, 1.43)	0.68 (0.21, 2.18)
Prolonged PTT	0.22 (0.02, 1.90)	0.51 (0.09, 2.92)
Elevated AST	0.37 (0.04, 3.68)	0.24 (0.03, 2.23)
Elevated ALT	0.66 (0.09, 4.94)	0.30 (0.03, 3.35)

Adverse events, AEs; confidence intervals, CI; PT, prothrombin time; PTT, partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine transaminase

* Please refer to Table 1 for the criteria used to determine laboratory AEs and SAEs