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

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Background

- Piperacillin-tazobactam (Pip-Tazo) is FDA approved to treat susceptible bacteria in adults and children two months of age and older.[1]
- Pip-Tazo is often used to treat infants with nosocomial infections and gram negative rod sepsis, however limited information is known about its safety in infants.[1]

Objectives

- Leverage a previously published population PK model[2] to simulate piperacillin exposure in infants.
- Relate simulated exposure to the safety of Pip-Tazo in infants from a large electronic health record (EHR) database.

Methods

- We identified infants exposed to Pip-Tazo discharged from 333 neonatal intensive care units managed by the Pediatrix Medical Group between 1997 and 2012.
- Typical values for CL and V were simulated according to the following relationships: CL (L/h)=0.080·WT·(PMA/33)$^{1.76}$ and V(L)= 0.42·WT, respectively, where WT is body weight (kg) and PMA is postmenstrual age (weeks). The coefficient of variation for the CL interindividual variability was 37%, whereas no inter-individual variability in volume was assumed.[2]
- The safety of Pip-Tazo was evaluated by identifying adverse events listed in the FDA product label including: seizure, rash, hypernatremia (>155 mmol/L), hypokalemia (<3mmol/L), prolonged prothrombin time (>15 seconds) and partial thromboplastin time (>50 seconds), low hematocrit (<37%), leukopenia (<5000/mm^3), thrombocytopenia (<100/mm^3), elevated creatinine (>1.7 mg/dL), and elevated AST (>600 U/L) and ALT (>225 U/L).[1]
- AE's were captured from the second day until the end of drug exposure and clinical AE's were reported as the percentage of infants with the event and laboratory AE's were reported as the percentage of days with the event.
- We used multivariable logistic regression to evaluate the association for the area under the curve at steady state from 0 to tau ($AUC_{ss,0-\tau}$) and the presence of any clinical or laboratory AE controlling for gestational age.
- Odds ratios (95% confidence intervals) comparing the third (> 1657.6) versus the first tertiles (<1039.7) for $AUC_{ss,0-\tau}$ were presented.

Results

- This study included 747 infants who received 839 courses of Pip-Tazo for a total of 5901 infant days.

Table 1. Demographics

	N=747
Gestational age, weeks	
< 26	18%
26–28	27%
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	27%
7–29	54%
30–59	18%
Race/ethnicity	
White	19%
African American	9%
Hispanic	70%
Other	2%
Male	57%
Inborn	74%
Cesarean delivery	66%
Small for gestational age	17%

Table 2. Simulated Piperacillin Exposure

GA (weeks)	PNA (days)	N	Piperacillin Dose (mg/kg/day)	$AUC_{ss,\ 0-\tau}$ (mg*hr/L)
< 32	<14	183	200 (100, 320)	1471 (681, 3055)
	≥ 14	333	240 (100, 400)	1233 (511, 2495)
≥ 32	<14	257	250 (100, 400)	1236 (472, 3229)
	≥ 14	38	300 (150, 400)	966 (475, 1941)
Total		839	225 (100, 400)	1303 (520, 2959)

* Median (5th, 95th percentiles)

Table 3. Relating Exposure ($AUC_{ss,\ 0-\tau}$) with Clinical and Laboratory AE's

	Patients (%) or Infant Days (%)	Adjusted Odds Ratio (95% Confidence Interval)
Clinical AE's (Patients, %)		
Seizures	1.3%	5.60 (2.74, 11.46)
Rash	0.8%	1.45 (0.77, 2.73)
Serum electrolytes (Infant days, %)		
Hypernatremia	0.4%	0.77 (0.53, 1.12)
Hypokalemia	0.8%	0.46 (0.34, 0.63)
Renal dysfunction (Infant days, %)		
Elevated creatinine	0.5%	0.59 (0.33, 1.06)
Complete blood count (Infant days, %)		
Thrombocytopenia	13.5%	1.03 (0.90, 1.19)
Leukopenia	1.5%	0.79 (0.65, 0.97)
Low Hematocrit	5.4%	1.09 (0.95, 1.26)
Coagulation (Infant days, %)		
Prolonged partial thromboplastin time	0.2%	0.06 (0.01, 0.26)
Liver Dysfunction (Infant days, %)		
Elevated AST	0.1%	0.83 (0.38, 1.80)
Elevated ALT	0.1%	2.91 (1.26, 6.72)

Conclusions

- In this study, Pip-Tazo had a favorable safety profile in infants, which was consistent with previous reports.[3,4]
- In the cohort studied, the incidence of seizures (1.3%) and elevated ALT (0.1%) were uncommon but both were associated with piperacillin exposure.
- Additional studies to further assess this relationship are warranted.
- Combining PK modeling with EHR data is a feasible and novel method to evaluate drug safety in infants.

References

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