

Ampicillin Exposure and Odds of Seizures in a Large Cohort of Hospitalized Neonates

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Background

- Ampicillin is the most commonly used drug in the neonatal intensive care unit (NICU), with pharmacokinetic (PK) variability and limited evaluations of its safety
- Seizures are a known adverse event of beta-lactams and occur in adults with serum ampicillin Cmax >140 mcg/mL
- Ampicillin dosing or exposure associated with seizures in neonates have not been described

Objective

- Evaluate the association of ampicillin simulated exposure with seizures in hospitalized neonates

Methods

- Retrospective cohort study from 348 NICUs managed by the Pediatrix Medical Group between 1997 and 2012
- Inclusion criteria:
 - 24-41 weeks gestational age
 - Exposure to ampicillin in the first 25 days of life
- Exclusion criteria:
 - <50 mg/kg/day of ampicillin
 - Serum creatinine >2.5 mg/dL
- Definitions:
 - Exposure - the maximum steady-state ampicillin concentration (Cmax), and dichotomized into low (≤140 mcg/mL) vs. high (>140 mcg/mL) exposure
 - Seizure - any new seizure diagnosis made after the first through the last day of exposure to ampicillin
- Primary outcome:
 - New diagnosis of seizures while exposed to ampicillin
- We simulated Cmax at steady-state using the intermittent infusion equation and a previously described population PK model in neonates: $V(L) = 0.399 * WTKG$ and $CL(L/hr) = 0.078 * WTKG * (0.6/SCR)^{0.428} * (PMA/37)^{1.34}$, combined with clinical characteristics and dosing information
- We stratified neonates according to gestational and postnatal age at ampicillin exposure
- We calculated odds of seizures on days of high vs. low ampicillin exposure using multivariable logistic regression with GEE methodology, controlling for the following covariates:
 - Gestational age in weeks (GA), postnatal age in days (PNA), and presence of a positive cerebrospinal fluid (CSF) culture

Results

- 132,026 neonates received ampicillin for a total of 654,373 days
- 790 neonates (0.6%) seized while exposed to ampicillin
- Median ampicillin dose and simulated Cmax were 99 mg/kg(interquartile range (IQR) 51, 100) and 257mcg/mL(IQR 164, 291)
- The adjusted odds of seizure were higher on days of simulated ampicillin Cmax>140mcg/mL: odds ratio=1.50 (95% confidence interval 1.17, 1.91, p=0.001)

Table 1. Clinical Data

	Seizure n=790	No seizure n=131,236	P-value
Gestational age (weeks)	37 (32, 39)	35 (32, 38)	<0.001
Birth weight (grams)	2824 (1796, 3341)	2390 (1691, 3100)	<0.001
Postmenstrual age (weeks)	37 (33, 39)	35 (32, 38)	<0.001
Postnatal age (days)	2 (1, 3)	2 (1, 5)	<0.001
Positive CSF culture, no (%)	19 (2%)	103 (<1%)	<0.001
Serum Creatinine (mg/dL)	0.9 (0.7, 1.2)	0.7 (0.6, 0.9)	<0.001
Simulated Cmax (mcg/mL)	273 (165, 294)	257 (164, 292)	<0.001

Median (25, 75%tile) unless otherwise indicated.

Table 2. Pharmacokinetic Data

	Seizure n=791 days	No seizure n=653,582 days	P-value
Ampicillin dose (mg/kg/day)	99 (51, 100)	99 (51, 100)	0.06
Simulated Cmax (mcg/dL)	273 (165, 294)	257 (164, 292)	<0.001
Simulated Cmax >140 (mcg/dL), no(%)	721 (91%)	576,559 (88%)	0.01

Median (25, 75%tile) unless otherwise indicated.

Results

Figure 1. Simulated Cmax by Ampicillin Dose (mg/kg/day) (Red Line: Cmax=140mcg/dL)

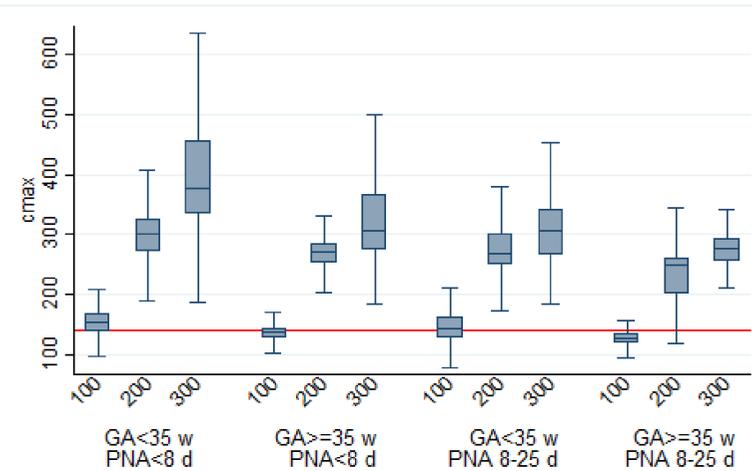
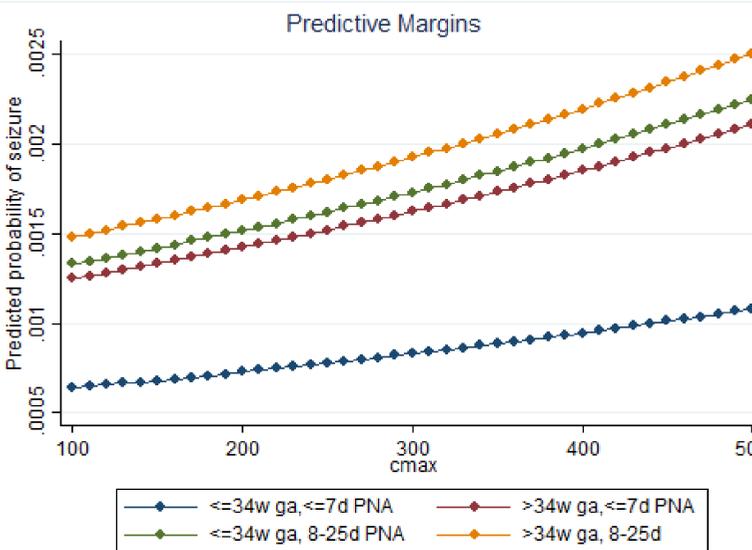


Figure 2. Predicted Seizure Probability by Simulated Cmax



Conclusions

- Seizures are rare in neonates receiving ampicillin, but odds increase with higher simulated Cmax
- Improved ampicillin dosing based on GA/PNA should be used to limit Cmax

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