Electronic Health Records and Pharmacokinetic Modeling to Assess the Relationship between Ampicillin Exposure and Seizure Risk in Neonates

Christoph P. Hornik, MD, MPH[1,2], Daniel K. Benjamin, Jr, MD, MPH, PhD[1,2], P. Brian Smith, MD, MPH, MHS[1,2], Michael J. Pencina, PhD[1], Adriana H. Tremoulet, MD, MAS[3], Edmund V. Capparelli, PharmD[4,5], Jessica E. Ericson, MD[6], Reese H. Clark, MD[7], and Michael Cohen-Wolkowiez, MD, PhD[1,2], on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network*

Objective To evaluate the relationship between ampicillin dosing, exposure, and seizures.

Study design This was a retrospective observational cohort study of electronic health record (EHR) data combined with pharmacokinetic model derived drug exposure predictions. We used the EHR from 348 Pediatrix Medical Group neonatal intensive care units from 1997 to 2012. We included all infants 24-41 weeks gestational age, 500-5400 g birth weight, first exposed to ampicillin prior to 25 days postnatal age. Using a 1-compartment pharmacokinetic model and EHR data, we simulated maximum ampicillin concentration at steady state (C_{maxss}, μg/mL) and area under the concentration time curve from 0 to 24 hours (AUC_{24}, μg*h/dL). Using multivariable logistic regression, we evaluated association between ampicillin dosing, exposure, and seizures as documented in the EHR.

Results We identified 131 723 infants receiving 134 041 courses of ampicillin for 653 506 infant-days of exposure. The median daily dose was 200 mg/kg/d (25th, 75th percentile; 100, 200). Median C_{maxss} and AUC_{24} were 256.6 μg/mL (164.3, 291.5) and 2593 μg*h/dL (1917, 3334). On multivariable analysis, dosing was not associated with seizures. However increasing C_{maxss} (OR = 1.10, 95% CI 1.03, 1.17) and AUC_{24} (OR 1.11, 95% CI 1.05, 1.18) were associated with increased odds of seizures.

Conclusions In this cohort of hospitalized infants, higher ampicillin exposure was associated with seizures as documented in the EHR. *(J Pediatr 2016;178:125-9).*

Ampicillin, a beta-lactam antibiotic, is the most commonly used medication in hospitalized infants.[1] Over 10% of all North Americans receive the drug during infancy, and over 90% of premature infants are exposed to the drug.[1-3] Despite its frequent use, the current Food and Drug Administration (FDA) ampicillin label does not include dosing or safety information for infants.[4]

Based on the FDA's pediatric study decision tree, ampicillin labeling would follow the complete extrapolation pathway and be supported by pediatric pharmacokinetic (PK) and safety data.[5,6] Despite the long history of ampicillin investigations in infants, no well-powered, dedicated safety study has been conducted recently. Prior studies are older, have a small sample size, and focus on efficacy instead of safety.[7-10] The many challenges of clinical trials in infants, including subject vulnerability, enrollment difficulties, and blood sampling limitations make it unlikely that a well-powered, dedicated, prospective safety study will be conducted.[6]

Given the challenges of conducting traditional safety trials in infants, alternative approaches are needed.[11,12] One approach proposed here is to combine predicted ampicillin exposure with dosing and clinical data routinely collected in the electronic health record (EHR) of a large cohort of hospitalized infants. Given the wide variability of ampicillin PK in infants, EHR data alone is unable to characterize the exposure safety relationship of the drug.[13] To overcome this limitation, we simulated ampicillin exposures using a population PK model developed from a cohort of infants enrolled in a PK study conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Pediatric Trials Network.[14]

AUC_{24}	Area under the concentration time curve from 0 to 24 hours
C_{maxss}	Maximum daily serum concentration of ampicillin at steady state
CSF	Cerebrospinal fluid
EHR	Electronic health record
FDA	Food and Drug Administration
GA	Gestational age
GEEs	Generalizing estimating equations
PK	Pharmacokinetic
PNA	Postnatal age

From the [1]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC; [2]Department of Pediatrics, Duke University School of Medicine, Durham, NC; [3]Department of Pediatrics, University of California, San Diego, La Jolla, CA; [4]Deparment of Biostatistics and Bioinformatics, Duke University, Durham, NC; [5]Skaggs School of Pharmacy, University of California, San Diego, La Jolla, CA; [6]Department of Pediatrics, Penn State University, Hershey, PA; and [7]Pediatrix-Obstetrix Center for Research and Education, Sunrise, FL

*List of additional Best Pharmaceuticals for Children Act—Pediatric Trials Network members is available at www.jpeds.com (Appendix 1).

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We hypothesized that higher predicted ampicillin exposure would be associated with increased odds of seizures. We focused on seizures as a rare but severe side effect previously described in adults.[15-17] Seizure risk theoretically may be even higher in neonates, but, to date, risk has not been well described.[18] We further hypothesized that because of the variability of ampicillin PK in this population, currently employed dosing regimens would not be associated with seizure risk.

Methods

We used a database derived from the EHR populated by clinicians on all infants cared for by the Pediatrix Medical Group in 348 neonatal intensive care units in North America from 1997 to 2012. Data on multiple aspects of care were entered into a shared EHR to generate admission and daily progress notes and discharge summaries, and then transferred to the Pediatrix clinical data warehouse for quality improvement and research purposes.[19] The study was approved by the Duke Institutional Review Board without the need for written informed consent.

Our inclusion criteria matched the characteristics of the clinical trial cohort used to develop the ampicillin population PK model.[14] We included infants 24-41 weeks gestational age (GA) and 500-5400 g birth weight first exposed to ampicillin prior to a postnatal age (PNA) of 25 days. We included only ampicillin courses started prior to 25 days PNA and completed prior to 60 days PNA, with a daily ampicillin dose ≥50 mg/kg/d (to avoid including prophylactic dosing regimens), and with a most recent serum creatinine of 0.2-2.5 mg/dL prior to the first dose of ampicillin.[14]

Each ampicillin course was stratified based on the infant's GA at birth and PNA on the first day of therapy into 1 of 4 categories: ≤ 34 weeks GA and ≤7 days PNA; >34 weeks GA and ≤7 days PNA; ≤34 weeks GA and 8-25 days PNA; and >34 weeks GA and 8-25 days PNA. These categories were chosen to match the stratification used in the development of the ampicillin PK model to predict exposures and optimal dosing.[14] We extracted dosing frequency and total daily dose of ampicillin from the EHR, and weight-normalized daily doses rounded to the nearest 25 mg/kg/d. We then categorized the dose received as optimal if it was equal to previously published dosing recommendation: for infants ≤34 weeks GA and ≤7 days PNA: 50 mg/kg/dose every 12 hours; for infants ≤34 weeks GA and 8-25 days PNA: 75 mg/kg/dose every 12 hours; and for infants >34 weeks GA and <25 days PNA: 50 mg/kg/dose every 8 hours.[14] Total daily doses that were above or below the optimal dosing were categorized as higher than, or lower than optimal dosing. We defined bacteremia and meningitis as the presence of a positive blood culture with any organism not typically considered a contaminant and any cerebrospinal fluid culture during or up to 3 days prior to each ampicillin course. We defined a seizure as any new clinical diagnosis of seizure documented in the EHR and made after the first and up to the last day of ampicillin exposure. Details about the mode of diagnosis including electroencephalography, video electroencephalography, or involvement of pediatric neurologist were not routinely captured in the EHR. We defined inotropic support and mechanical ventilation on each infant-day as any exposure to an inotropic drug (amrinone, dobutamine, dopamine, epinephrine, norepinephrine, or milrinone) or to any form of mechanical ventilation.

Statistical Analyses

We used medians with 25th and 75th percentiles and counts with percentages to describe study variables. We compared distributions of variables across groups using Wilcoxon rank sum and χ^2 tests of association where appropriate. We simulated the maximum daily serum concentration of ampicillin at steady state (C_{maxss}) and the area under the concentration time curve from 0 to 24 hours (AUC_{24}) using the intermittent infusion equation, clinical characteristics, and dosing information combined with a previously described 1-compartment population PK model in infants: Volume of distribution (L) = 0.399 * weight and clearance (L/h) = 0.078 * weight * (0.6/serum creatinine)$^{0.428}$ * (postmenstrual age/37)$^{1.34}$. Between-subject variability in ampicillin clearance and residual variability were included in the simulations. We also calculated cumulative C_{maxss} and AUC_{24} by adding up the daily predicted values within each treatment course. We compared C_{maxss} and AUC_{24} on days with and without a new diagnosis of seizures using univariable logistic regression with generalizing estimating equations (GEEs) to account for the clustered nature of the data by infant. To characterize the association between dosing and seizures, we performed multivariable logistic regression at the infant-day, course, and infant level adjusting for total daily dose of ampicillin, GA at birth, PNA, need for mechanical ventilation, need for inotropic support, and presence of a positive blood or cerebrospinal fluid (CSF) culture. When necessary (day and course level regressions), we used GEEs to account for the clustered nature of the data by infant. Total daily dose was modeled both as a continuous variable or categorized as optimal, lower, or higher dosing.[14] To evaluate the association between daily C_{maxss} and AUC_{24}, and seizures, we performed separate multivariable logistic regression models using GEEs to account for the clustered nature of the data by infant. The following covariates were included in the final models: GA at birth, PNA, need for mechanical ventilation, need for inotropic support, and presence of a positive blood or CSF culture. We included C_{maxss} and AUC_{24} as continuous variables or as continuous variables normalized to their respective SD (absolute value/SD) in separate models. We performed a sensitivity analyses by dichotomizing C_{maxss} as ≤140 μg/mL vs >140 μg/mL based on prior seizure thresholds in adults.[16] Finally, we report the cumulative C_{maxss} and AUC_{24} reached on the first day of a new seizure. We calculated the median PNA at which seizures were first diagnosed and compared cumulative C_{maxss} and cumulative AUC_{24} with the values registered at the same PNA in infants who did not experience seizures using Wilcoxon rank sum tests. We correlated daily dose and C_{maxss} and AUC_{24} using Spearman rank correlation coefficient. We used Stata 13.1 (StataCorp, College Station, Texas) to perform all statistical analysis and considered P values of <.05 statistically significant.