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

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Abstract

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

Study design—Retrospective observational cohort study of electronic health record (EHR) data combined with pharmacokinetic model derived drug exposure predictions. EHR from 348 Pediatric Medical Group neonatal intensive care units from 1997 to 2012. 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 her data, we simulated maximum ampicillin concentration at steady state (C_{maxss} , $\mu\text{g/mL}$) and area under the concentration time curve from 0 to 24 hours (AUC_{24} , $\mu\text{g}\cdot\text{h/dL}$). 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/day (25th, 75th percentile; 100,

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200). Median C_{maxss} and AUC_{24} were 256.6 $\mu\text{g/mL}$ (164.3, 291.5) and 2593 $\mu\text{g}\cdot\text{h/dL}$ (1917, 3334). On multivariable analysis, dosing was not associated with seizures. However increasing C_{maxss} [Odds ratio (OR) = 1.10, (95% confidence interval (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.

Keywords

Infants; Ampicillin; Seizure; Exposure; Dosing

Ampicillin, a beta-lactam antibiotic, is the most commonly used medication in hospitalized infants.(1) Over 10% of all 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 rather than 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 (NICHD) Pediatric Trials Network.(14)

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 (BW) 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/day (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; >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/day. 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; 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 (EEG), video EEG, 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 Chi square 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) = $0.399 * \text{weight}$ and Clearance (L/hr) = $0.078 * \text{weight} * (0.6/\text{serum creatinine})^{0.428} *$

(postmenstrual age/37)^{1,34}. Between-subject variability in ampicillin clearance and residual variability were included in the simulations. We also calculated cumulative $C_{\max ss}$ and AUC_{24} by adding up the daily predicted values within each treatment course. We compared $C_{\max ss}$ and AUC_{24} on days with and without a new diagnosis of seizures using univariable logistic regression with generalizing estimating equations (GEE) 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 GEE 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 $C_{\max ss}$ and AUC_{24} , and seizures, we performed separate multivariable logistic regression models using GEE 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 $C_{\max ss}$ and AUC_{24} as continuous variables or as continuous variables normalized to their respective standard deviation (absolute value/standard deviation) in separate models. We performed a sensitivity analyses by dichotomizing $C_{\max ss}$ as ≤ 140 $\mu\text{g/mL}$ versus >140 $\mu\text{g/mL}$ based on a prior seizure thresholds in adults.⁽¹⁶⁾ Finally, we report the cumulative $C_{\max ss}$ 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 $C_{\max ss}$ and cumulative AUC_{24} to the values registered at the same PNA in infants who did not experience seizures using Wilcoxon rank sum tests. We correlated daily dose and $C_{\max ss}$ and AUC_{24} using Spearman's rank correlation coefficient. We used Stata 13.1 (College Station, TX) to perform all statistical analysis and considered a $p < 0.05$ statistically significant.

RESULTS

We identified 131,723 infants who received 134,041 courses of ampicillin for a total of 653,506 infant-days of exposure. The median GA and BW were 35 weeks (25th, 75th percentile 32, 38) and 2394 g (1692, 3102) (Table I). Most infants were male [75,728/131,723 (58%)], born via cesarean [71,636/131,723 (54%)], and inborn [108,682/131,723 (83%)]. CSF cultures were obtained in 10,498/131,723 (8%) of infants, and were positive in 105/10,498 (1%).

The median postnatal age and postmenstrual age on the day of first ampicillin exposure were 1 day (1, 2), and 35 weeks (32, 38). The median treatment course duration was 4 days (3, 7). The median daily dose was 200 mg/kg/day (100, 200) with a maximum of 450 mg/kg/day. The most common dosing frequencies were every 12 hours [123,890/134,041 (92%)] and every 8 hours [9914/134,041 (7%)], with every 6 and every 4 hour dosing used in $<1\%$ of treatment courses. Optimal dosing was used in a minority of treatment courses [20,891/134,041 (16%)], with most treatment courses using a higher dose [92,257/134,041 (69%)]. Infants ≥ 34 weeks GA and ≥ 7 days PNA at the time of first ampicillin exposure were more likely to receive optimal dosing compared with all other infants [16,349/60,683

(27%) vs. 4542/73,358 (6%), $p<0.001$]. This distribution of dosing did not differ between infants who did and those who did not have a CSF culture obtained (13% optimal, 68% higher, 20% lower for infants with CSF culture vs. 16% optimal, 69% higher, 15% lower for infant without CSF culture, $p=0.34$).

Seizures were rarely diagnosed while on ampicillin [781/653,506 (<1%) of days exposed to ampicillin and 780/134,041 (1%) of courses]. Seizures typically were diagnosed early in the ampicillin treatment course [median 3 days (2, 4)], and were significantly more common in infants with meningitis [19/171 (11%) vs. 761/131,552 (0.6%), $p<0.01$]. The most common organisms isolated from the CSF or blood were group B *Streptococcus* (48% in CSF, 68% in blood) and *Escherichia coli* (12% in CSF, 13% in blood); distribution of organisms did not differ by seizure diagnosis ($p=0.713$ for CSF and $p=0.972$ for blood). Seizures also were diagnosed more commonly in more mature and older infants.

Dosing-safety relationship

The median daily dose of ampicillin on days with and without seizures did not differ significantly [200 mg/kg/day (100, 200) vs. 200 mg/kg/day (125, 200), $p=0.39$]. The prevalence of seizures was lower on days with optimal versus higher or lower dosing [103/106,451 (0.1%) vs. 524/449,340 (0.12%) vs. 154/97,715 (0.16%), $p<0.001$]. On multivariable analysis, the odds of seizures did not increase with increasing total daily dose of ampicillin (odds ratio (OR) = 0.99 (95% confidence interval (CI); 0.99, 1.01). Similarly, the odds of seizure did not differ significantly between courses with higher versus optimal or lower versus optimal dosing [OR = 0.95 (95% CI 0.76, 1.18) and OR = 1.20 (95% CI 0.92, 1.58)], respectively. Results also were similar when regressions were performed at the treatment course or infant level, rather than the infant-day level.

Exposure-safety relationship

Ampicillin exposure was evaluated using $C_{\max ss}$ and AUC_{24} (Table II). As expected, $C_{\max ss}$ and AUC_{24} increased with increased dosing (Spearman's Rank correlation 0.76 ($p<0.001$) for $C_{\max ss}$ and 0.63 ($p<0.001$) for AUC_{24}). Both median $C_{\max ss}$ and AUC_{24} were higher in the higher dosing group and lower in the lower dosing group when compared with the optimal dosing group (all $p<0.001$). Similarly, the proportion of days with $C_{\max ss}>140$ $\mu\text{g/mL}$ was lowest on days with lower dosing and highest on days with higher dosing [48,893/97,715 (9%) for lower dosing vs. 80,160/106,451 (75%) for optimal dosing vs. 447,883/449,340 (99%) for higher dosing, $p<0.001$].

$C_{\max ss}$ and AUC_{24} were higher on days with seizures compared with days without seizures (Table II). Seizures were more likely to be diagnosed on days with $C_{\max ss}>140$ $\mu\text{g/mL}$ [719/576,936 (0.12%) vs. 62/76,570 (0.08%), $p<0.001$]. The median cumulative $C_{\max ss}$ and AUC_{24} at a PNA of 3 days (median age of seizure diagnosis) did not differ significantly between infants who were diagnosed with a seizure on that day compared with those who did not [$C_{\max ss}$: 560 $\mu\text{g/mL}$ (460, 828) vs. 773 $\mu\text{g/mL}$ (438, 843, $p=0.26$; AUC_{24} : 7412 $\mu\text{g}\cdot\text{h/mL}$ (5121, 9697) vs. 7666 $\mu\text{g}\cdot\text{h/mL}$ (5162, 10030), $p=0.44$]. Results were similar when comparisons were stratified by presence or absence of meningitis diagnosis.

On adjusted analysis, the odds of seizure were higher with increasing $C_{\max ss}$ and AUC_{24} (Table III). 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).

DISCUSSION

Our study linked predicted ampicillin exposure with safety events in infants by combining EHR data with predicted ampicillin exposures from a PK model. We found that higher ampicillin exposure, as measured by $C_{\max ss}$ and AUC_{24} , was associated with increased odds of seizures, but ampicillin dosing alone was not. Together, these findings are consistent with the known high variability of ampicillin PK in infants, and suggest that lowering exposure, not just dosing, is necessary to improve the drug's safety profile.

Despite its frequent use, adverse events associated with ampicillin in infants mostly have been reported sporadically in retrospective efficacy studies.(20–22) Although the majority of reported events were non-specific and benign (rash, transient hypoglycemia), a potentially more serious adverse event, seizures, was reported in 2% of infants exposed to ampicillin in the first 3 days of life.(20) Seizures also are listed as adverse events associated with ampicillin in commonly used infant drug dosing references but not on the FDA label.(23, 24) In our study, we found an overall low incidence of seizures (<1%), which increased slightly with gestational and postnatal age. Our use of EHR data allowed us to reach a sample size that would not be achievable in a traditional prospective safety trial in infants. With this sample size, we had sufficient power to detect subtle but potentially meaningful differences in seizures rates by gestational and postnatal age, and by the presence of absence of meningitis and bacteremia.

Studies in adults have shown that the risk of seizure increases with CSF and plasma exposure to beta-lactam antibiotics.(15–17) A key strength of our study is the ability to include predicted ampicillin plasma exposures in our analyses to assess the association between ampicillin exposure and seizure risk in infants. Using a population PK model of ampicillin in neonates,(14) we found that predicted $C_{\max ss}$ and AUC_{24} generally was high, and both were associated with increased risk of seizures. This was true for $C_{\max ss} > 140$ $\mu\text{g/mL}$, a cut-off previously identified in critically ill adults, and when examining the distribution of exposure as a continuous variable. Conducting an adequately powered prospective safety study of ampicillin and measuring drug plasma levels would not be feasible in infants. An alternative, more focused approach to studying the safety of drugs in infants previously was published for the antibiotic meropenem(25, 26).

Combining data from a small, 200 infant prospective safety study with EHR data from over 5000 infants, we reported an overall favorable safety profile, with a relatively low incidence of seizures particularly when compared with imipenem. This information was submitted to the FDA in consideration for label change. We did not perform meropenem exposure predictions given the lack of variability in drug dosing and exposures observed in the PK trial(27). This assumption however would not hold true for ampicillin and many other drugs, necessitating the approach taken here. Our novel, opportunistic study design is cost-

effective, efficient, and minimizes risk by applying the PK model to routinely collected clinical data without the need for prospective plasma sampling.

Ampicillin dosing was not associated with seizure risk. This is an essential, albeit not surprising finding, likely related to the high variability of exposures observed at the same dose. Ampicillin PK properties are known to vary widely in infants. Renal clearance of ampicillin in particular, is known to vary with gestational and postnatal age.(14, 28) In the recently conducted Pediatric Trials Network opportunistic PK trial of ampicillin, standard of care dosing led to a wide range of observed ampicillin concentrations (<50 µg/mL to >400 µg/mL).(14) Despite this variability, the surrogate efficacy endpoint targets generally were met (% time above minimum inhibitory concentration). How this variability affects ampicillin's safety profile however, has not been shown previously. Even though seizures generally occurred more frequently in the higher dosing range, our results suggest that for certain infants, standard of care dosing practices can lead to levels of exposure associated with seizures.

The strengths of our study included its novel, cost-effective, efficient, and minimal-risk design. Nevertheless, our study is not without limitations. Most importantly, the dosing and safety data is derived from an EHR, which has not undergone the development and scrutiny of prospective trial database. Seizures were diagnosed based on clinical documentation, and no standardized protocols were used to make this diagnosis. This methodology most likely underestimates the seizure prevalence that would have been detected using electroencephalography, but may be a more realistic depiction of daily clinical practice. In order to estimate ampicillin exposures, we had to restrict our cohort to meet the inclusion and exclusion criteria of the ampicillin PK trial population.(14) This lead to the exclusion of infants with the most profound alteration in renal function, and those exposed to ampicillin later in life. Lastly several other risk factors for seizures in neonates were not available in the electronic health record for inclusion in the multivariable analyses. This included a family history of febrile seizures or the presence of a fever, degree of illness, or other event on the day of seizure diagnosis.

Reliance on age based dosing recommendations alone may be insufficient to avoid this rare, but serious adverse event, such as seizures. Newer dosing recommendations may provide more predictable ampicillin exposure. Until this has been proven in future studies, clinical vigilance and dose adjustment are necessary to improve ampicillin's safety profile.

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List of Abbreviations

AUC	Area under the curve
CSF	Cerebrospinal fluid

EHR	Electronic health record
GA	Gestational age
PK	Pharmacokinetic
PNA	Postnatal age

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Appendix 1

Additional members of the Best Pharmaceuticals for Children Act – Pediatric Trials Network include

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Appendix 2

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Table 1

Clinical data on the first day of ampicillin exposure

	Infants with seizure		All infants N=131,723
	Yes N=780	No N=130,943	
Gestational age at birth (weeks)	37 (33, 39)	35 (32, 38)	35 (32, 38)
Birth weight (g)	2833 (1815, 3343)	2390 (1692, 3100)	2394 (1692, 3102)
Postmenstrual age (weeks)	37 (33, 39)	35 (32, 38)	35 (32, 38)
Postnatal/gestational age, N (%)			
7 days & 34 weeks	233 (30)	60,004 (46)	60,237 (46)
7 days & >34 weeks	529 (68)	68,691 (52)	69,220 (53)
8–25 days & 34 weeks	10 (1)	1538 (1)	1548 (1)
8–25 days & >34 weeks	8 (1)	710 (1)	718 (<1)
Serum creatinine (mg/dL)	0.9 (0.7, 1.2)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)
Positive blood culture, N (%)	51 (7)	1927 (2)	1978 (2)
Positive CSF culture, N (%)	17 (2)	88 (<1)	105 (<1)
Positive blood or CSF culture, N (%)	52 (7)	1962 (2)	2014 (2)

Data presented as median (25th, 75th percentile) unless indicated. CSF=cerebrospinal fluid.

Table 2

Ampicillin exposure by infant-day

	Seizure		P-value *
	Yes N=781	No N=652,725	
C _{maxss} (µg/mL)	273.1 (165.4, 294.0)	256.6 (164.3, 291.5)	0.01
C _{maxss} >140 µg/mL, n (%)	705 (92)	567,274 (88)	0.001
AUC ₂₄ (µg*h/mL)	2706 (2024, 3460)	2593 (1917, 3334)	<0.001

Data presented as median (25th, 75th percentile) unless indicated. C_{maxss}=Maximum concentration at steady state; AUC₂₄=area under the concentration time curve from 0–24 hours.

* : p-values come from univariable logistic regression with GEE methodology.

Table 3

Adjusted odds of seizure.

	Odds Ratio[*] (95% confidence interval)
C _{maxss} (µg/mL)	1.01 (1.01, 1.02)
C _{maxss} (SD) ^{**}	1.10 (1.03, 1.17)
C _{maxss} >140 µg/mL	1.76 (1.35, 2.30)
AUC ₂₄ (µg*h/mL)	1.01 (1.01, 1.02)
AUC ₂₄ (SD) ^{**}	1.11 (1.05, 1.18)

^{*} adjusted for gestational and postnatal age, bacteremia, meningitis, mechanical ventilation, and inotropic support;

^{**} Odds ratio represents change in 1 standard deviation of C_{maxss} and AUC₂₄ respectively. C_{maxss}=Maximum concentration at steady state; AUC₂₄=area under the concentration time curve from 0–24 hours.