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Cefazolin Pharmacokinetics in Premature Infants

Stephen J. Balevic, MD[1,2], **P. Brian Smith, MD, MPH**[1,2], **Daniela Testoni, MD, PhD, MHS**[3], **Huali Wu, PhD**[1], **Kim L.R. Brouwer, PharmD, PhD**[4], **Kanecia O. Zimmerman, MD, MPH**[1,2], **Nazario D. Rivera-Chaparro, MD**[5], **Daniel K. Benjamin Jr, MD, PhD**[1,2], **Michael Cohen-Wolkowiez, MD, PhD**[1,2]

[1]Duke Clinical Research Institute, Durham, NC

[2]Department of Pediatrics, Duke University Medical Center, Durham, NC

[3]Escola Paulista de Medicina-Universidade Federal de São Paulo, São Paulo, Brazil

[4]UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC

[5]Novant Health Medical Group, Charlotte, NC

Abstract

Objective: Pharmacokinetic (PK) data to guide cefazolin dosing in premature infants is virtually non-existent. Therefore, we aimed to characterize cefazolin PK in infants aged ≤32 weeks of gestation at birth.

Study Design: We conducted a prospective, open-label PK and safety study of cefazolin in infants ≤32 weeks gestation from a University Medical Center. We administered intravenous cefazolin and collected both timed and scavenged blood samples. We analyzed data using non-linear mixed effect modeling and simulated several dosage regimens to achieve target concentrations against methicillin-susceptible *Staphylococcus aureus*.

Results: We analyzed 40 samples from 9 infants and observed that premature infants had lower clearance and greater volume of distribution for cefazolin compared to older children. The median (range) individual Bayesian estimates were 0.03 L/h/kg (0.01-0.08) for clearance and 0.39 L/kg (0.31-0.52) for volume.

Conclusion: Simulations suggested reduced cefazolin dosing based on postmenstrual age achieve target concentrations and potentially reduce unnecessary exposure.

Keywords

Cefazolin; Pharmacokinetics; Premature

Corresponding Author: Michael Cohen-Wolkowiez, MD, PhD, Duke Clinical Research Institute, 2400 Pratt St, Durham NC 27705, Phone: (919) 668-8812, Fax: (919) 613-6878, michael.cohenwolkowiez@duke.edu.

Introduction

Suboptimal dosing in premature infants can occur when dosage regimens do not account for physiologic changes affecting drug disposition [1]. Cefazolin is a cephalosporin approved in children >1 month of age to treat indicated susceptible infections [2] at an initial total daily dose of 25-50 mg/kg [2]. Maximum cefazolin effect occurs when free concentrations are > minimum inhibitory concentrations (MIC) for 60-70% of the dosing interval [3]. The surrogate pharmacodynamic marker of concentration at 75% of the dosing interval (C75) can predict target attainment [1].

Cefazolin is commonly used off-label in premature infants. While weight and postnatal age affect cefazolin pharmacokinetics (PK) [4], data in premature infants are virtually non-existent. In children 0.8-10 years of age, estimates of volume of distribution (Vz) for cefazolin are 0.08-0.263 L/kg and estimates of clearance are 0.048-0.1 L/hr/kg [5-7]. Cefazolin binds to albumin, with mean (range) protein binding estimates of 49% (17-78) in neonates [8]. Because up to 80% of cefazolin undergoes glomerular filtration and active tubular secretion as intact drug, the reduced renal function in premature infants may substantially increase cefazolin exposure.

Methods

Study design

We conducted a prospective, open-label PK and safety study (NCT00850122) in accordance with the Declaration of Helsinki. Duke University and Universidade Federal de São Paulo/ Hospital São Paulo IRBs approved the protocol. We obtained signed informed consent from all participants. We determined sample size based on the ability to observe a serious adverse event.

Population

Between 2013-2015, we enrolled infants aged ≤32 weeks at birth, >48 hours of age, and <121 days of age who 1) had a suspected systemic infection, 2) were receiving cefazolin for prophylaxis, or 3) were receiving cefazolin to treat a systemic infection. We excluded infants with a history of β-lactam anaphylaxis, cefazolin exposure ≤1 month from enrollment, or serum creatinine >1.7 mg/dL.

Dosing and sample collection

We administered cefazolin via intravenous (IV) infusion over 30 minutes to infants with postnatal age ≤28 days (25 mg/kg Q12h) and >28 days (25 mg/kg Q8h) [6-8]. We collected up to 4 scavenged blood samples throughout the dosing interval supplemented with up to 6 timed (non-scavenged) blood samples (200 μl each) as follows: Q8h dosing: 0.5-1h, 1-3h, 6-8h after the 1st and 4th, 5th, or 6th dose; Q12h dosing: 0.5-1h, 1-3h, 6-12h after the 1st and 4th dose.

Analytics

We quantified cefazolin plasma concentration using high performance liquid chromatography/mass spectrometry (HPLC-MS/MS). We prepared calibration standards and quality-control samples using drug-free human EDTA plasma, with a linear concentration range from 0.5-500 μg/mL and lower limit of quantitation of 0.5 μg/mL.

Population PK analysis

We analyzed data with NONMEM 7 using the first-order conditional estimation method with interaction algorithm. We explored 1-, and 2-compartment structural models and proportional, additive, and proportional-plus-additive residual error models. We included weight as a covariate for structural parameters by estimating or fixing weight on clearance to 0.75, and fixing weight on volume to 1. We assessed model fit using diagnostic plots, parameter precision, and objective function value (OFV).

Model-building

We investigated continuous covariates for their influence on PK parameters, including postmenstrual age (PMA), postnatal age (PNA), gestational age (GA), and serum creatinine. We included concomitant gentamicin, ampicillin, and amikacin as categorical covariates. We plotted individual participant deviations from the typical population parameter values (ETAs) against covariates and evaluated those with a graphical relationship for inclusion in the model. We defined the threshold for significance of a single covariate as a reduction of OFV by >3.84 ($p<0.05$) and used backward-elimination when >1 covariate was statistically significant.

Model evaluation

We performed prediction-corrected visual predictive checks (pcVPCs) for the final model by generating 1000 Monte Carlo simulation replicates/time point. We used the dosing and covariate values from the study population to simulate concentrations, and compared simulated to observed results. To evaluate parameter precision, we generated 95% confidence intervals using nonparametric bootstrapping (1000 replicates).

Dosing simulation

We simulated total and free cefazolin concentrations using the final population PK model, the Empirical Bayesian Estimates (EBEs), and clinical data for each participant. We estimated free concentrations using fraction unbound (fu) 0.34 and 0.68 [8]. For each participant, we simulated several dosage regimens infused over 0.5 hours, using a primary target of simulated free steady-state C75 >1x MIC of cefazolin (4 μg/mL) against methicillin-susceptible *Staphylococcus aureus* (MSSA) [9]. We also simulated free steady-state C75 >5x MIC as a surrogate marker for excessive exposure.

Results

Participant characteristics

Clinical characteristics of the infants are described in Table 1, with individual subject data in supplemental Table 1. Altogether, 41 samples were obtained from 9 infants; 1 concentration below the quantifiable limit was excluded. For scavenged samples, the median (range) time from sample collection to freezing was 2.8 (0.7-7.9) hours. The median (range) of infant characteristics were: PNA 16 days (3-91); PMA 30.7 weeks (25.7-44.6); weight 1.3 kg (0.7-2.8); albumin 3.0 g/dL (2.6-3.0); and serum creatinine 1.0 mg/dL (0.1-1.4). Using appropriate racial/ethnic growth parameters [10], two infants (22.2%) were small for gestational age with birth weight less than the tenth percentile for gestational age based on sex. We obtained 6 (2-6) samples per infant, and the median cefazolin concentration was 59.3 mcg/mL (10.1-183). Six infants received Q12h dosing, and 3 infants received Q8h dosing. All infants received treatment with concomitant antimicrobials, most commonly ampicillin (5/9), gentamicin (4/9), and amikacin (3/9).

PK model development

A summary of PK model building is outlined in Table 2. A 1-compartment model provided the best fit based on the goodness of fit and pcVPC plots, although the model over-predicted at concentrations >80 mcg/mL. Univariable addition of PMA, PNA, GA, or creatinine to the clearance model did not result in a significant decrease in OFV (i.e. OFV reduction <3.84). However, PMA <34 weeks, PMA <37 weeks, PNA <17 days, and PNA <25 days as categorical covariates on clearance significantly reduced OFV. Of these, PMA <37 weeks on clearance had optimal performance based on visual inspection of the clearance vs. PMA relationship and the reduction in OFV (−4.2). Although PNA <17 days had greater reduction in the OFV (−4.3), we implemented the PMA cutoff of <37 weeks on clearance because 1) cefazolin is cleared predominantly through the kidneys, and 2) nephrogenesis finishes before 37 weeks [11]. We did not observe a relationship between volume and PMA, PNA, or GA. Addition of amikacin or ampicillin as a covariate on clearance resulted in a significant drop in OFV (4.5 and 4.3, respectively, $p<0.05$) but was not included due to confounding, whereby subjects with high creatinine received concomitant ampicillin while subjects with normal creatinine received amikacin. Further, addition of concomitant medications did not reduce the OFV once PMA was included as a covariate on clearance.

The final model revealed that 96% of bootstrap datasets converged to >2 significant digits. The median of bootstrap fixed effects parameter estimates were within 17% of population estimates from the original dataset for all parameters. The pcVPC revealed 10% (4/40) of observed concentrations were slightly outside the 90% prediction interval. The median (range) individual EBEs were 0.03 L/h/kg (0.01-0.08) for clearance and 0.39 L/kg (0.31-0.52) for volume. The relative standard error was 44% for clearance and 9% for volume. Other PK parameter estimates are outlined in Table 3.

Dosing simulation

Simulations predicted that target attainment was sensitive to protein binding for some dosage regimens for each of the 9 subjects (Table 4). The regimen used in the clinical study

(25 mg/kg Q12h for PNA ≤28 days, 25 mg/kg Q8h >28 days) resulted in 100% attainment of >1x MIC with wide ranges of protein binding, but with 56-78% of subjects having free C75 >5x MIC. Conversely, regimen 5 also resulted in 100% attainment of >1x MIC, but with fewer subjects (11-22%) having exposure >5x MIC.

Discussion

We developed a 1-compartment PK model to characterize cefazolin disposition in infants ≤32 weeks of gestation. Despite a small cohort, our model had good performance based on pcVPCs and parameter precision, with only a slight tendency for over-prediction. We found that PMA (categorical) was a significant covariate for cefazolin clearance. However, unlike other reports [4], PMA (continuous) was not significant, probably due to low sample size and limited age distribution. Because cefazolin is renally filtered and actively secreted, the association between PMA and clearance may reflect renal maturation [11]. The median EBE clearance estimate in our study was 0.03 L/h/kg (range 0.01-0.08), approximately one-half that reported for a 9-day-old infant weighing 2720 g (0.068 L/kg/hr) [4]. Lower clearance estimates may be due to differences in study populations; the median GA in our study was 29.1 weeks, compared with 37 weeks elsewhere [4]. As expected from immature renal function, the cefazolin clearance for premature infants in our study was significantly lower than clearance reported in older children (0.048-0.1 L/hr/kg) [5-7]. Furthermore, the cefazolin EBE volume (0.39 L/kg) was higher than that reported in older children (0.08-0.263 L/kg) [5-7], likely because premature infants have a higher percentage of total body water.

Using the dosage regimen administered during this study, 100% of infants would obtain free C75 >1x MIC; further, more than half would have exposure >5x MIC for MSSA regardless of estimated unbound fraction. Simulations predict that a reduced dosage regimen (6 mg/kg IV Q12h for PMA <37 weeks, 25 mg/kg IV Q8h for PMA ≥37 weeks and <120 days) would also result in 100% attainment >1x MIC; however, target attainment may be lower if deep tissue infections are targeted. Notably, this dosing is lower than other published simulations [4], likely from modeling differences (e.g., using unbound drug concentrations), simulation endpoint, and the degree of prematurity/critical illness of the underlying population. Although estimating free concentration using binding percentages has limitations [4], we simulated free concentrations using a wide range of published binding estimates to determine dosing implications across the binding spectrum.

Infants in the study received cefazolin for a variety of clinical indications, including prophylaxis or treatment for a systemic infection. Therefore, it is possible that infants receiving cefazolin for treatment a systemic infection had more physiologic alterations that could impact PK. Despite this potential limitation, all 9 infants were critically ill with a median (range) of 7 (4-12) comorbid medical conditions.

There are some limitations of our study. Notably, our sample size was small and therefore our power to detect covariates was limited. In addition, the infants in our study had a limited distribution of gestational ages and were recruited from a Hispanic/Latino population. As a

result, our proposed dosing regimen should be prospectively tested in a larger population before widespread clinical use.

In conclusion, premature infants exhibited a lower clearance and greater volume of distribution for cefazolin compared with older children. Dosage regimen simulations suggested reduced doses of cefazolin based on postmenstrual age may achieve target concentrations in neonates, and potentially reduce unnecessary drug exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

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Table 1.

Clinical Characteristics

Characteristic	Value[1,2]
Postnatal age (days)	16 (3 – 91)
Postmenstrual age (weeks)	30.7 (25.7 – 44.6)
Gestational age at birth (weeks)	29.1 (25.3 – 31.6)
Body weight (kg)	1.3 (0.7 – 2.8)
Females	3 (33%)
Albumin (g/dL)	3.0 (2.6 – 3.0)
Total bilirubin (mg/dL)	6.9 (3.2 – 33.2)
Serum creatinine (mg/dL)	1.0 (0.1 – 1.4)
Race	
White	3 (33%)
Black	6 (67%)
Ethnicity	
Hispanic or Latino	9 (100%)
Dose (mg/kg)	24.9 (23.3 – 25.2)
Duration of cefazolin infusion (h)	0.5 (0.5 – 0.7)

[1]Continuous data represented as median (range) and categorical data is represented as n (%).

[2]Where applicable, data was at the time of first PK sample.

Table 2.

Model Building Steps

Description	Model	OFV	ΔOFV[1]
Univariable analysis			
Base Model[2]	$CL = \theta_{CL} \times (WT/1.3)^{1.7}$	255.1	-
PMA on CL, maturation function	$CL = \theta_{CL} \times (WT/1.3)^{0.52} \times (PMA^{3.7}/(54.5\ ^{3.7}+PMA^{3.7}))$	253.5	−1.6
PMA on CL	$CL = \theta_{CL} \times (WT/1.3)^{0.31} \times (PMA/30.7)^{3.8}$	253.4	−1.7
PNA on CL	$CL = \theta_{CL} \times (WT/1.3)^{1.1} \times (PNA/16)^{0.25}$	254.5	−0.6
GA on CL	$CL = \theta_{CL} \times (WT/1.3)^{1.7} \times (GA/29.1)^{0.002}$	255.1	0
SCR on CL	$CL = \theta_{CL} \times (WT/1.3)^{1.1} \times (SCR/1.0)^{-0.50}$	252.6	−2.6
PMA<34 PMA<34 weeks, PMAC=1 (n=6) PMA≥34 weeks, PMAC=0 (n=3)	$CL = \theta_{CL} \times (WT/1.3)^{1.38} \times 0.71^{PMAC}$	251.2	−3.9
PMA<37 **PMA<37 weeks, PMAC=1 (n=7)** **PMA≥37 weeks, PMAC=0 (n=2)**	$CL = \theta_{CL} \times (WT/1.3)^{0.82} \times 0.24^{PMAC}$	250.9	−4.2
PNA<25 PNA<25 days, PNAC=1 (n=6) PNA≥25 days, PNAC=0 (n=3)	$CL = \theta_{CL} \times (WT/1.3)^{0.73} \times 0.33^{PNAC}$	251.2	−3.9
PNA<17 PNA<17 days, PNAC=1 (n=5) PNA≥17 days, PNAC=0 (n=4)	$CL = \theta_{CL} \times (WT/1.3)^{0.73} \times 0.33^{PNAC}$	250.8	−4.3
Ampicillin on CL	$CL = \theta_{CL} \times (WT/1.3)^{0.63} \times 0.31^{Ampicillin}$	250.8	−4.3
Amikacin on CL	$CL = \theta_{CL} \times (WT/1.3)^{0.80} \times 4.01^{Amikacin}$	250.6	−4.5
Multivariable analysis			
PMA<37, ampicillin on CL	$CL = \theta_{CL} \times (WT/1.3)^{0.46} \times 0.39^{PMAC} \times 0.48^{Ampicillin}$	249.1	−1.8
PMA<37, amikacin on CL	$CL = \theta_{CL} \times (WT/1.3)^{0.82} \times 1.15^{PMAC} \times 4.49^{Amikacin}$	250.6	−0.3

[1]Change in OFV for the univariable analysis was relative to the base model; the multivariable analysis is relative to the intermediate PMA<37 on CL model.

[2]$V = \theta_V$ for all models.

Abbreviations: OFV: objective function value; CL: Clearance (L/h); V: Volume of distribution (L); PMA: Post-menstrual age (weeks); PNA: Post-natal age (days); SCR: Serum creatinine (mg/dL); GA: gestational age; WT: weight; Theta (θ): value of a parameter in a population that is updated during parameter estimation.

Table 3.

Population PK parameters.

Parameter	Estimate	RSE (%)	Shrinkage (%)	Bootstrap CI		
				2.5%	Median	97.5%
Structural PK Model						
CL (L/h, 1.3kg)	0.099	44	-	0.011	0.104	0.183
V (L, 1.3kg)	0.507	9	-	0.424	0.501	0.600
WT on CL	0.817	73	-	0.008	0.937	3.885
PMA<37 on CL	0.243	55	-	0.064	0.283	3.070
Inter-individual Variability (IIV) (%CV)						
CL IIV	51.8	141	13	0.5	43	117
V IIV	15.6	99	19	0.5	16	28
Residual Variability						
Proportional Error (%)	19.0	29	12	11	18	23

Abbreviations: CL: Clearance; PMA: Postmenstrual age; RSE: Relative standard error; V:Volume of distribution; WT:Weight; CV: Coefficient of Variation

Table 4.

Simulated concentrations of free cefazolin at 75% of the dosing interval after different dosage regimens.

	C75, Free[1] >1x MIC fu=0.34	C75, Free >5x MIC fu=0.34	C75, Free >1x MIC fu=0.68	C75, Free >5x MIC fu=0.68
	Percent of Subjects Achieving Target			
Regimen 1 25 mg/kg IV Q12h (PMA <37 weeks) 25 mg/kg IV Q8h (PMA ≥37 weeks & <120 days)	100	56	100	78
Regimen 2 25 mg/kg IV Q24h (PMA <37 weeks) 25 mg/kg IV Q12h (PMA ≥37 weeks & <120 days)	78	11	100	44
Regimen 3 25 mg/kg IV Q24h (PMA <37 weeks) 25 mg/kg IV Q8h (PMA ≥37 weeks & <120 days)	100	11	100	44
Regimen 4 12.5 mg/kg IV Q24h (PMA <37 weeks) 25 mg/kg IV Q12h (PMA ≥37 weeks & <120 days	44	11	100	11
Regimen 5 6 mg/kg IV Q12h (PMA <37 weeks) 25 mg/kg IV Q8h (PMA ≥37 weeks & <120 days	100	11	100	22

[1] C75, free – Free concentration at 75% of the dosing interval calculated using total C75 and unbound fraction for cefazolin.

Abbreviations: fu: fraction unbound; IV: intravenous; PMA: postmenstrual age; MIC: Minimum inhibitory concentration.