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Objectives

The objective of this study was to determine the pharmacokinetics of cefuroxime in children undergoing cardiopulmonary bypass (CPB) for cardiovascular surgery.

Design

A prospective study.

Setting

A tertiary pediatric teaching hospital.

Participants

Infants and children undergoing CPB were enrolled in the study.

Intervention

An initial dose (mean, 24.2 ± 1.6 mg/kg) of cefuroxime was administered before surgical incision, and a second dose (mean, 14.4 ± 7.9 mg/kg) was administered in the CPB prime solution. Serial blood samples were obtained before, during, and after the CPB process. Samples were shipped on dry ice to the analytic laboratory and concentrations determined by a validated high-performance liquid chromatography method. A 2-compartment pharmacokinetic model was fitted to the data using maximum a priori–Bayesian estimation, with weight as a covariate. Monte Carlo simulations of a single-dose (25 mg/kg pre-CPB) approach and a 2-dose (25 mg/kg pre- and 12.5-mg/kg prime solution dose) approach were performed.

Measurements and Main Results

Fifteen subjects (9 males/6 females) were enrolled in the study, with median (range) age and weight of 11 (3-34) months and 9.5 (4.5-15.4) kg, respectively. The median (range) duration of CPB was 136 (71-243) minutes. Median and range cefuroxime pharmacokinetic parameters were as follows: maximum concentration (Cmax) dose, 1: 328 (150-512) μg/mL; systemic clearance, 0.050 (0.041-0.058) L/h/kg; steady-state volume of distribution, 0.213 (0.081-0.423) L/kg; volume of distribution in the central compartment, 0.081 (0.046-0.162) L/kg; and elimination half-life, 3.76 (1.03-6.81) hours. The median 8-hour post–dose-simulated cefuroxime concentrations were 26.5 and 16.0 mg/L for the 2-dose and single-dose regimens, respectively.

Conclusion

Manufacturers recommend that pediatric doses of cefuroxime (25-50 mg/kg) can be used in infants and children undergoing CPB to maintain adequate serum concentrations for surgical-site infection prophylaxis. A second intraoperative dose, administered through the CPB circuit, provides no additional prophylactic advantage.

Surgical-site infections (SSIs) account for approximately 16% of hospital-acquired infections. [1] Of particular concern for patients undergoing cardiac surgery are deep sternal wound infections or mediastinitis after procedures with a median sternotomy. Sternal wound infections occur in 5% of all children after median sternotomy. [2] Associated mortality is significant and has been reported to be as high as 60% in adults although there are little comparable data for children. [3] Estimates of sternal wound infections in pediatric patients after cardiac surgery vary from 3% for superficial sternal infections, 2% for deep sternal infections, to 0.04% to 3.9% for mediastinitis. [2] [4] [5] [6] Incidence of sternal wound infection has been shown to be greater in neonates (5.5%) versus older children (0.5%), and was associated with increased morbidity and mortality in the neonatal group. [7]

Incisional cellulitis and fever are common presenting signs of sternal wound infection in children. This likely is secondary to interruption of the skin barrier and further complicated by the placement of percutaneous devices that then may be colonized and potentially infected along the tract. In multiple series, staphylococcal species (*Staphylococcus aureus* and *Staphylococcus epidermidis*) were the most common infecting pathogens. [2] [3] [8] [9] [10] For antimicrobial prophylaxis for cardiac surgery, a cephalosporin, such as cefazolin or cefuroxime, is the preferred agent unless a high probability of methicillin-resistant *S aureus* (MRSA) is suspected or the patient has a β-lactam allergy. [11] The minimum inhibitory concentration (MIC) value for staphylococcal species susceptible to parenteral cefuroxime is ≤8 µg/mL. [12]

A review of the literature shows limited pediatric data describing cardiopulmonary bypass (CPB) effects on prophylactic antibiotic therapy; none of which describes cefuroxime. [13] [14] Children may have a greater hemodilution effect from CPB initiation than adults, and extrapolating from adult cefuroxime data creates inaccuracy. [15] Definitive recommendations for redosing of intraoperative antibiotic prophylaxis because of CPB effects are not available for children undergoing surgery for congenital heart defects. To adequately prevent SSI and subsequent morbidity and mortality, an additional intraoperative cefuroxime dose could be required if the cefuroxime serum concentration falls to below desired concentrations. The objective of this study was to determine the pharmacokinetics of cefuroxime in pediatric patients undergoing cardiac surgery with CPB. The authors also sought to evaluate whether doses currently used achieved appropriate concentrations for protection against potential pathogens.

Methods

Fifteen children between 1 month and 3 years of age who required CPB for their surgical repair were included. Subjects were excluded if they had an allergy to β-lactam antibiotics; were born at less than 36 weeks' gestational age or were older than 3 years (3 years and 0 days); had an anticipated CPB time of less than 30 minutes; or had a history of culture positive for MRSA, ventricular-assist device therapy, or cardiac transplantation. This study was conducted after

approval from the institutional review board at Indiana University-Purdue University, Indianapolis, IN. Informed consent for the study was obtained from the parent or guardian at the time of surgical consent.

Demographic data collected on all patients included sex, age, weight, serum creatinine, cardiac defect, and repair. Temperature, perfusion priming volume, time on CPB, coldest temperature, and modified ultrafiltration volume were collected from perfusion and anesthesia records. The contents of the CPB prime solution could vary per patient and contain, but were not limited to, plasmalyte, albumin, methylprednisolone, sodium bicarbonate, blood, and cefuroxime.

Cefuroxime (target dose, 25 mg/kg) was administered through an intravenous catheter within 1 hour before skin incision. A second dose of cefuroxime (target dose, 12.5 mg/kg) was administered in the CPB prime solution. Both doses were administered according to institutional standard. Seven serial blood samples were obtained before, during, and after CPB at the time points described in Table 1 . The times at which these samples were taken were targeted at the times described although the actual times varied depending on the clinical situation. The first sample was obtained by using excess blood from the routine baseline preoperative laboratory samples. The other blood samples (5 mL each) were obtained via arterial hemodynamic catheters, which all patients receive as a standard of cardiovascular surgical care, or directly from the CPB circuit (considered postcircuit). Blood samples were obtained by either the anesthesiologist or perfusionist while the patient remained in the operating room and by a pediatric intensive care unit nurse after surgery. Blood samples were collected into heparinized-evacuated blood-collection tubes. Samples were mixed and centrifuged, and the plasma was collected and stored frozen at −70°C. Samples were shipped on dry ice to the analytic laboratory for analysis and processed within 4 weeks of receipt.

Table 1
Timing of Blood Samples for the Determination of Cefuroxime Pharmacokinetics

Sample	Intraoperative Event	Approximate Time Relation to Cefuroxime Dosing
1	Before cefuroxime dose	−12 to 72 hours
2	Heparin administration	+70 minutes
3	5 minutes after initiation of CPB	+90 minutes
4	Initiation of rewarming	+180 minutes
5	Separation from bypass	+210 minutes
6	5 minutes after protamine administration	+230 minutes
7	Arrival in the intensive care unit	+260 to 290 minutes

Plasma concentrations of cefuroxime were determined by a modified reverse-phase high-performance liquid chromatography method with ultraviolet detection (214 nm) per previously described techniques. [16] [17] Samples were processed by protein precipitation with 4% perchloric acid with tinidazole (10 μg/mL, Sigma, St. Louis, MO) used as the internal standard. Five hundred microliters of solution were added to 250 μL of sample, standard, or spiked control. The samples then were vortexed for 30 seconds followed by centrifugation at 3.0 g for 15 minutes. A 50-μL portion of supernatant was injected directly onto the high-performance liquid chromatography column, and the peak-area ratio of cefuroxime-to-internal standard was analyzed. The only modification to the analytic procedure was the use of 2 Onyx monolithic C18 analytic columns (50 × 4.6 mm) placed in series (Phenomenex, Torrance, CA). The range of

assay linearity was 5.0 to 200 μg/mL ($r \geq 0.998$, n = 7); specimens with concentrations >200 μg/mL were diluted with blank pooled human plasma and reassayed. The limit of assay detection with a 50-μL injection volume was 1.0 μg/mL. The within-day (n = 5) and between-day (n = 7) coefficients of variation for spiked control specimens (5, 50, and 200 μg/mL) were ≤3.4% and ≤8.2%, respectively.

Initial estimates of cefuroxime pharmacokinetics were determined by noncompartmental techniques using the individual concentration-time data. After visualizing the concentration-time profile and the 2-exponential decline characteristics, a 2-compartment model was chosen as the structural pharmacokinetic model. Equations describing a 2-compartment, pharmacokinetic model were fitted to each subject's cefuroxime concentration-time data using ADAPT 5 [18] with the weighted least-squares estimator. The pharmacokinetic parameters estimated were as follows: Vc, the apparent volume of distribution in the central compartment; Vp, the apparent volume of distribution in the peripheral compartment; Cld, the distribution clearance between the central and peripheral compartment; and Cls, systemic clearance, which was assumed not to change over the course of the entire study period. The weighting scheme used was 1/(observed concentration) ^{2} . After completion of the initial weighted least-squares fitting process, the impact of weight as a coavariate on pharmacokinetics was investigated. The authors observed a significant relationship between weight and pharmacokinetic parameters. The same structural model was fit to the data this time using the maximum a priori (MAP)-Bayesian estimator in ADAPT 5. The initial pharmacokinetic parameter estimates with their associated intersubject variability were used as initial MAP-Bayesian estimators, with Vc and Cls normalized for subject weight. The variance model assumed the standard deviation of the residuals was linear with increasing concentrations using the following equation: $f(V) = [y_{int} + m(y)]^2$, where y_{int} is the y-intercept of the residual plot and m is the slope of the line. The y-intercept was fixed at one-half of the lower limit of detection for the cefuroxime assay. The slope (m) was estimated in each individual subject. The same pimary pharmacokinetic parameters were estimated with this model. The secondary parameters estimated in this model were apparent steady-state volume of distribution (Vss), elimination rate constant, and elimination half-life (t1/2). Secondary parameters were calculated by standard equations. Model fits were assessed by visual inspection of the predicted versus measured data and the distribution of the weighted residuals.

One hundred simulations were performed using the MAP-Bayesian–generated pharmacokinetic estimates using 2 dosing schemes: (1) an initial 25-mg/kg intravenous dose followed by a 12.5-mg/kg prime dose (study dose), and (2) an initial 25-mg/kg intravenous dose. Each simulation consisted of using the mean and variance of the pharmacokinetic parameters (Vc, Vp, Cls, and Cld) from the final pharmacokinetic analysis as described previously, with the parameters listed in Table 2 .

Table 2
Subject Demographics

Subject	Sex	RACHS	Minimal Temperature (°C)	Age (Months)	Dose 1 (mg/kg)	Dose 2 (mg/kg)	Pre-weight (kg)	Post-weight (kg)	Height (cm)	Prime Vol (mL)	Duration of CPB (min)
1	M	3	28	19	24.8	6.76	11.1	11.1	81	830	124

Subject	Sex	RACHS	Minimal Temperature (°C)	Age (Months)	Dose 1 (mg/kg)	Dose 2 (mg/kg)	Pre-weight (kg)	Post-weight (kg)	Height (cm)	Prime Vol (mL)	Duration of CPB (min)
2	M	2	28	17	24.3	14.6	10.3	10.3	71	570	125
3	M	3	27	4.5	23.2	12.5	5.3	5.4	65	515	168
4	F	3	26.6	11	26.7	None	7.9	9.0	72	600	165
5	F	3	28	18	22.1	11.5	10.6	11.3	85	565	151
6	M	3	30	27	25.4	12.3	13.6	13.8	92	825	75
7	F	2	26.1	9	23.8	11.9	8.4	8.4	76	620	163
8	M	4	25	9	24.2	12.1	8.7	9.1	67	715	405
9	M	4	28	10	23.6	28.3	10	10.6	76	450	93
11	F	3	28	23	27.0	12.6	10.2	10.2	81	675	154
12	M	3	30	11	25.6	12.6	7.8	7.8	74	630	124
13	F	4	26	12	23.3	29.1	9.5	10.3	74	1000	107
14	F	3	27	6	23.7	27.0	7.1	7.4	66	650	108
15	M	3	26	3	20.9	11.5	4.5	4.8	62	670	120
16	M	3	29	33.6	24.4	12.7	15.4	15.4	94	770	93
		Mean	27.5	14.2	24.2	14.4	9.36	9.66	75.7	672.3	145
		SD	1.5	8.65	1.59	7.94	2.83	2.80	9.51	139.7	77.5
		Median	28	11.0	24.2	12.5	9.50	10.2	74.0	650	124

Demographic study data were collected and reported by descriptive statistics. Regression analysis was used to determine the relationship between weight and the initial pharmacokinetic parameter fits. Statistical analysis was performed using Graph Pad Prism (v 5.2; Graph Pad Software Inc., La Jolla, CA). Statistical significance was defined as a *p* value of <0.05.

Results

Sixteen subjects provided informed consent and were enrolled. Because of a protocol violation, 15 subjects (9 male subjects and 6 female subjects) completed the study. The subject demographics are shown in Table 2 . As shown in Table 2 , all but 1 subject received 2 doses of cefuroxime. No adverse effects were reported related to cefuroxime.

The mean cefuroxime pharmacokinetic parameters are shown in Table 3 . Individual cefuroxime plasma concentration-time curves, both observed and modeled data, in 6 representative subjects are shown in Figure 1 . As evidenced by this figure, there was good agreement between the fitted and observed data. The simulated cefuroxime concentration-time curves for the 2 cefuroxime dosing regimens are shown in Figure 2 . Median 8-hour postdose-simulated cefuroxime concentrations were 26.5 and 16.0 mg/L for the 2-dose and single-dose regimens, respectively.
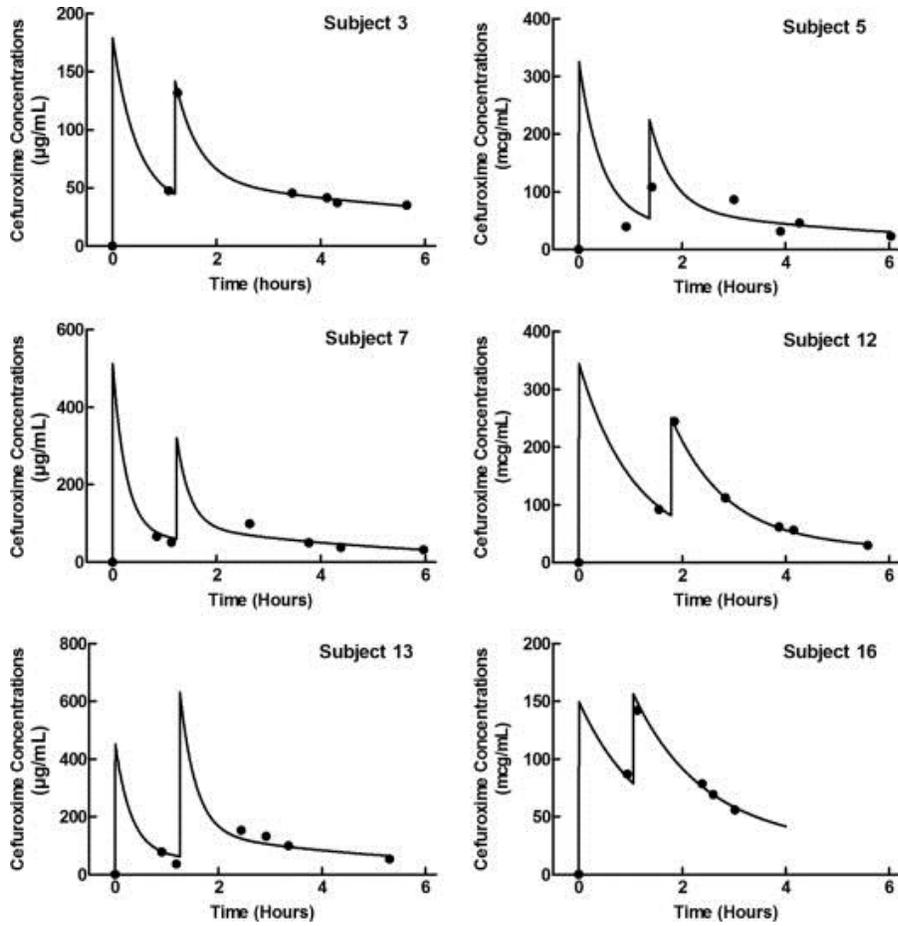
Fig 1

Representative individual observed and modeled cefuxoxime concentration-time curves in 6 subjects. Observed data are indicated by the closed circles and modeled data by the solid lines. Subjects 3, 7, and 12 were younger than 1 year of age and subjects 5, 13, and 16 were older than 1 year of age.
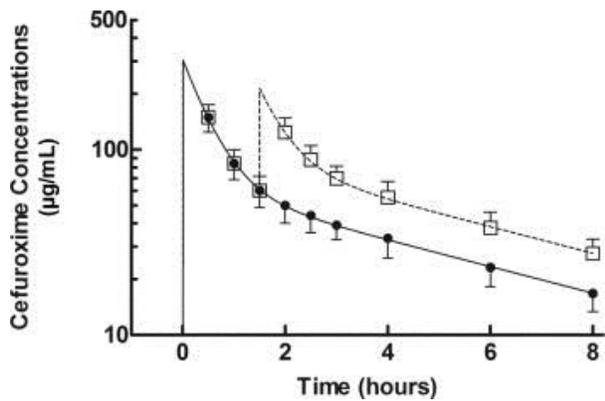

Fig 2

Simulated cefuroxime mean concentration-time profiles for 2 dosing regimens, a 25-mg/kg single dose (closed circles, solid line) and a 25-mg/kg initial dose followed by 12.5 mg/kg dose in the CPB prime solution (open boxes, dotted line).

Table 3

Mean and Standard Deviation (SD) Cefuroxime Pharmacokinetic Parameters

	Mean	SD
Cld (mL/min/kg)	43.9	40.2
Cls (mL/min/kg)	11.8	4.79
Vp (L/kg)	8.08	4.49
Vc (L/kg)	8.53	3.72
Vss (L/kg)	0.2104	0.0605
t½ (h)	19.1	3.51
β (h)	0.037	0.006
Cmax 1st dose (μg/mL)	328	102

Discussion

Cefuroxime is the preferred prophylactic antibiotic for pediatric cardiovascular surgery at the authors' institution. The initial dose is administered within 60 minutes of incision, and, in accordance with Surgical Infection Prevention (SIP) project and Society of Thoracic Surgeons (STS) recommendations, redosing is considered for procedures past 4 hours in length, regardless of the use of CPB. [11] [19] However, there are no published data regarding cefuroxime pharmacokinetics during pediatric cardiac surgeries requiring CPB and no pediatric-specific recommendations for the redosing of cefuroxime in these procedures. Pharmacokinetic differences observed in children when compared with adults make extrapolating adult literature difficult. [20]

CPB is a multiphased process with potential to alter the pharmacokinetic properties of a variety of medications including antibiotics. [15] [21] Prolonged CPB time has been linked to increased infection risk, thus making optimization of antibiotic prophylaxis critical. [2] [22] Caffarelli et al showed inadequate cefazolin serum concentrations after single prophylactic cefazolin doses for cardiac surgeries requiring longer than 120 minutes on CPB. [23] In the present study population, the average time on CPB was 145 minutes, making this an important factor. CPB-related hemodilution, as a result of the administration of blood and primer solution, decreases total serum concentration of medications through altering the volume of distribution of drugs. [26] [27] This effect has been shown with cephalosporins. [24] [25] Cefazolin concentrations decrease 32% to 62% as a result of the hemodilution effects of CPB. [14] [26]

Multiple studies have investigated the pharmacokinetics of cefuroxime during CPB although none has been performed in children, making comparison to the present results difficult. [16 27 28 29] However, it appears through the findings of Nascimento et al and Vuorisalo et al that cefuroxime pharmacokinetics in adults undergoing CPB are not altered by CPB. [27 29] The present findings in children are similar in that CPB does not appear to alter cefuroxime pharmacokinetics. Alternative cefuroxime dosing regimens, such as continuous infusion cefuroxime, have been studied in adults undergoing cardiac surgery, but making extrapolation to children is difficult because of the differences in dosing. [16]

Patients with congenital heart defects are a uniquely ill population with generally immature immune systems. [7] Children less than 1 year of age are the largest group undergoing surgery for congenital heart lesions. Fragility in the infant and postoperative period likely contribute to making deep sternal wound infections a life-threatening complication in this population. Additionally, infants requiring CPB may undergo deep hypothermic circulatory arrest resulting in decreased immune function. [30] Blunting of the immune response also may occur secondary to prolonged periods of diminished cardiac output. [31] Children with prolonged CPB time, long aortic cross-clamp time, long total operation time, and high-body-mass index have an increased risk for developing SSIs. [22 32] Optimizing the pharmacodynamic properties of perioperative antibacterial regimens is imperative to prevent infection.

The only study to examine cephalosporin pharmacokinetics in children undergoing CPB used cefazolin with gentamicin in infants less than 10 kg. [14] The investigators found that cefazolin distribution volume and elimination are altered by CPB, but that their dosing regimen (35 mg/kg) used, which is slightly higher than the recommended dosing range, remained effective for optimal infection prevention. [1 33] Comparing the present findings with those of Haessler et al [14] is difficult given the inherent differences in pharmacokinetic profiles between cefazolin and cefuroxime. Cefazolin is much more highly protein bound than cefuroxime. [34] Hemodilution-related decreases in circulating plasma proteins, specifically albumin and α-acid glycoprotein, may result in increased free drug and redistribution of drug to tissues as a result of CPB, and may lead to an overall increased free fraction of cefazolin. [21 24] This may not be applicable to cefuroxime given the minimal protein binding as compared with cefazolin.

In general, maximum bacterial killing for cephalosporins is observed when serum concentrations (unbound drug) are maintained above the MIC for 60% to 70% of the dosing interval, although a lower percentage may be required for staphylococcal species. [35] Cephalosporins, such as cefuroxime, are preferred antimicrobials for prophylaxis after cardiac surgery, in part because of the activity against *S aureus* and *S epidermis* . [11] The median 8-hour postdose-simulated cefuroxime concentrations were 26.5 and 16.0 mg/L for the 2-dose and single-dose regimens, respectively. Given the protein binding of cefuroxime of approximately 30%, either a 2-dose or single-dose intraoperative regimen would result in a serum concentration above the MIC for staphylococcal species for 100% of the dosing interval based on when the postoperative regimen would be the initiated model. [34] It appears as though a second intraoperative dose, administered through the CPB circuit, provides no additional prophylactic advantage. Currently, the manufacturer's recommended pediatric doses of cefuroxime (25-50 mg/kg) can be used in infants and children undergoing CPB to maintain adequate serum concentrations for SSI prophylaxis.

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