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# PHARMACOKINETICS OF CEFUROXIME ARE NOT SIGNIFICANTLY ALTERED BY CARDIOPULMONARY BYPASS IN CHILDREN



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## BACKGROUND

- Sternal wound infections occur in 5% of all children after median sternotomy.<sup>1</sup> Associated mortality is as high as 60% in adults.<sup>2</sup>
- Surgical Infection Prevention (SIP) Project recommends cefuroxime as a preferred antibiotic during cardiac surgery.<sup>3</sup>
- There are no published recommendations for the redosing of cefuroxime during pediatric cardiac surgeries requiring CPB. Cephalosporins display time-dependent PD, thus maintaining adequate concentrations throughout the entire surgery is essential.<sup>3</sup>
- CPB related hemodilution alters the volume of distribution of drugs, including cephalosporins in one study. CPB may also sequester drug.<sup>4,5</sup>
- Hypothermia during CPB may affect drug clearance via several mechanisms: decreasing hepatic and renal clearance and altered hepatic and renal blood flow.<sup>6</sup>
- There are limited data describing CPB effects on pediatric prophylactic antibiotic therapy, and none of which describe cefuroxime.<sup>7</sup>

## STUDY OBJECTIVE

To determine the pharmacokinetics of cefuroxime in pediatric patients undergoing open heart surgery with CPB.

## STUDY DESIGN

### Patients

- Patients (n=15) scheduled to undergo a surgical procedure requiring cardiopulmonary bypass at Riley Hospital for Children, Indianapolis, IN
- Study was approved by the Investigational Review Board at Indiana University-Purdue University-Indianapolis
- All parents/guardians provided written informed consent
- Exclusion Criteria:
  - Allergy to beta-lactam antibiotics
  - Age less than 36 weeks gestational age or greater than 3 years
  - Anticipated CPB time less than 30 minutes
  - History of culture positive for Methicillin-resistant Staphylococcus aureus
  - Ventricular assist device therapy
  - Cardiac transplantation

### Experimental Protocol

• Patients received two doses of cefuroxime as an IV bolus. The first dose of cefuroxime (target: 25 mg/Kg) was administered prior to surgical incision and a second dose (target: 12.5 mg/Kg) was administered in the CPB prime solution.

• Serial blood samples were obtained, before, during, and after CPB

• Blood samples were collected into heparinized blood collection tubes and the plasma was collected and stored frozen at -70 deg C until analysis. Samples were shipped on dry ice to the analytical laboratory.

### Determination of Plasma Cefuroxime Concentrations

• Cefuroxime concentrations were determined at the University of Cincinnati using reverse-phase HPLC assay with UV detection.

• The standard curves were linear, and the intra-run and inter-run coefficients of variation were  $\leq 10\%$ .

### Pharmacokinetic Analysis

• Candidate pharmacokinetic models were fit to the cefuroxime concentration-time data with ADAPT II using MAP Bayesian estimation.

• Model discrimination was accomplished by visual inspection of the predicted versus measured data, the distribution of the residuals, and the AIC.

• Two compartment model was chosen as the model of best fit.

• PK parameters:  $V_c$  and  $V_p$  (apparent volume of distribution in the central compartment and peripheral compartments respectively), and  $Cl_d$  and  $Cl_s$  (distribution clearance and systemic clearance, respectively).

• Secondary parameters: apparent steady-state volume of distribution ( $V_{ss}$ ), elimination rate constant and elimination half-life ( $t_{1/2}$ ) were calculated by standard equations.

• Simulations of a single-dose (25 mg/Kg pre-CPB) approach and a two-dose (25 mg/Kg pre and 12.5 mg/Kg prime solution dose) were performed.

## RESULTS

Table 1. Patient Characteristics, n=15

Age (months)	13.2 $\pm$ 9.2
Male (%)	53%
Weight (Kg)	9.4 $\pm$ 2.8kg
Duration of CPB (minutes)	145 $\pm$ 77.5

Table 2. Pharmacokinetic Parameters, n=15

	Dose 1 (mg/Kg)	Dose 1 Cmax (mg/L)	Dose 2 (mg/Kg)	Cl <sub>s</sub> (L/hr/Kg)	V <sub>ss</sub> (L/Kg)	V <sub>c</sub> (L/Kg)	t <sub>1/2</sub> (hrs)
Median	24.2	344	12.5	0.050	0.213	0.072	3.76
Range	20.9-26.7	150-512	0-29.1	0.041-0.058	0.081-0.423	0.046-0.162	1.03-6.81

Table 3. Simulated Cefuroxime Concentrations (mg/L)

	Cmax	C6 hour	C8 hour
Single Dose	340.3	23.2	16.0
Two Dose	340.3	38.5	26.5

## SUMMARY

• Currently recommended pediatric doses of cefuroxime (25-50mg/Kg) can be used in infants and children undergoing CPB to maintain adequate concentrations for surgical site infection prophylaxis.

• No indication of alteration in cefuroxime PK during CPB.

## CONCLUSIONS

Based upon the results of this study, the pharmacokinetics of cefuroxime are not altered by CPB.

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Figure. Simulation of cefuroxime concentrations based on median PK parameters in Table 2.

