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Pharmacokinetics of Cefuroxime are not Significantly Altered by Cardiopulmonary Bypass in Children

Chad A. Knoderer
Butler University, cknodere@butler.edu

Sarah A. Saft

Scott G. Walker

Daniel P. Healy

Kevin M. Sowinski

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

Chad A. Knoderer, PharmD • Sarah A. Saft, PharmD, BCPS • Scott G. Walker, MD •
Daniel P. Healy, PharmD, FCCP, FIDSA • and Kevin M. Sowinski PharmD, BCPS, FCCP

Butler University College of Pharmacy and Health Sciences, Indiana University School of Medicine, Purdue University, School of Pharmacy and Pharmaceutical Sciences and University of Cincinnati, Winkle College of Pharmacy • Indianapolis and West Lafayette, Indiana and Cincinnati, Ohio

BACKGROUND

•Sternal wound infections occur in 5% of all children after median sternotomy.[1] Associated mortality is as high as 60% in adults.[2]

•Surgical Infection Prevention (SIP) Project recommends cefuroxime as a preferred antibiotic during cardiac surgery.[3]

•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.[3]

• CPB related hemodilution alters the volume of distribution of drugs, including cephalosporins in one study. CPB may also sequester drug.[4,5]

• Hypothermia during CPB may affect drug clearance via several mechanisms: decreasing hepatic and renal clearance and altered hepatic and renal blood flow.[6]

• There are limited data describing CPB effects on pediatric prophylactic antibiotic therapy, and none of which describe cefuroxime.[7]

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 ≤ 10%.

Pharmacokinetic Analysis

•Candidate pharmacokinetic models were fit to the cefuroxime concentration-time date 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: Vc and Vp (apparent volume of distribution in the central compartment and peripheral compartments respectively), and Cld and Cls (distribution clearance and systemic clearance, respectively).

•Secondary parameters: apparent steady-state volume of distribution (Vss), elimination rate constant and elimination half-life (t1/2) were calculated by standard equations.

•Simulations of a single-dose (25 mg/Kg pre-CBG) 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 ± 9.2
Male (%)	53%
Weight (Kg)	9.4 ± 2.8kg
Duration of CPB (minutes)	145 ± 77.5

Table 2, Pharmacokinetic Parameters, n=15

	Dose 1 (mg/Kg)	Dose 1 Cmax (mg/L)	Dose 2 (mg/Kg)	Cls (L/hr/Kg)	Vss (L/Kg)	Vc (L/Kg)	$t_{1/2}$ (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

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

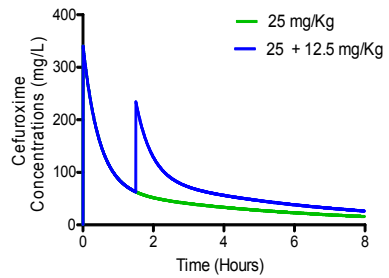

Table 3. Simulated Cefuroxime Concentrations (mg/L)

	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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