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.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 Institutional 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.

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

<table>
<thead>
<tr>
<th>Dose 1 (mg/Kg)</th>
<th>Dose 1 Cmax (mg/L)</th>
<th>Dose 2 (mg/Kg)</th>
<th>C1s (L/hr/Kg)</th>
<th>Vrs (L/Kg)</th>
<th>Vc (L/Kg)</th>
<th>l1/2 (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>24.2</td>
<td>344</td>
<td>12.5</td>
<td>0.050</td>
<td>0.213</td>
<td>0.072</td>
</tr>
<tr>
<td>Range</td>
<td>20.5-26.7</td>
<td>150-512</td>
<td>0-29.1</td>
<td>0.041-0.058</td>
<td>0.081-0.423</td>
<td>0.046-0.162</td>
</tr>
</tbody>
</table>

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 Clt and C1s (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.

CONCLUSIONS

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

REFERENCES