Plasma and Tissue Pharmacokinetics of Cefazolin in an Immature Porcine Model of Pediatric Cardiac Surgery

Todd Kilbaugh, Adam S Himebaugh, Theoklis Zaoutis, David Jobes, William Greeley, Susan C Nicolson and Athena F Zuppa

Abstract

Background: Surgical Site Infection (SSI) prevention for children with congenital heart disease is imperative and methods to assess and evaluate the tissue concentrations of prophylactic antibiotics are important to help maximize these efforts. The purpose of this study was to determine the plasma and tissue concentrations of standard-of-care peri-operative cefazolin dosing in an immature porcine model of cardiac surgery and cardiopulmonary bypass.

Methods: Piglets (3-5 days old) underwent either median sternotomy (MS) or cardiopulmonary bypass with deep hypothermic circulatory arrest (CPB+DHCA) and received standard of care prophylactic cefazolin for the procedures. Serial plasma and microdialysis sampling of skeletal muscle and subcutaneous tissue adjacent to the surgical site was performed. Cefazolin concentrations were measured, non-compartmental pharmacokinetic analyses were performed, and tissue penetration of cefazolin was assessed.

Results: Following the first intravenous dose, maximal cefazolin concentrations for plasma and tissue samples were similar between groups with peak tissue concentrations 15-30 minutes after administration. After the second cefazolin dose given with initiation of CPB, total plasma cefazolin concentrations remained relatively constant until the end of DHCA and then decreased while muscle and subcutaneous unbound cefazolin concentrations showed a second peak during or after rewarming. For the MS group, 60-67% of the intraoperative time showed tissue cefazolin concentrations greater than 16 μg/mL while this percentage was 78-79% for the CPB+DHCA group. There was less tissue penetration of cefazolin in the group that underwent CBP+DHCA (P=0.03).

Conclusions: The cefazolin dosing used in this study achieves plasma and tissue concentrations that should be effective against methicillin-sensitive Staphylococcus aureus but may not be effective against some gram-negative pathogens. The timing of cefazolin administration prior to incision and a second dose given during cardiopulmonary bypass may be important factors for achieving goal tissue concentrations.

Keywords: Cefazolin; Staphylococcus aureus; Pediatric; Escherichia coli; Enterobacter cloacae; Klebsiella pneumoniae

Abbreviations:

SSI: Surgical Site Infection; DHCA: Deep Hypothermic Circulatory Arrest; PK: Pharmacokinetics; CPB: Cardiopulmonary Bypass; MSSA: Methicillin-Sensitive Staphylococcus aureus; MRSA: Methicillin-Resistant Staphylococcus aureus; MD: Microdialysis; IF: Interstitial Fluid; HPLC-MS/MS: High-Performance Liquid Chromatography and Tandem Mass Spectrometry; Cmax: Maximum Plasma Concentration; Tmax: Time to Maximum Plasma Concentration; LLQ: Lower Limit of Quantification; AUC: Area Under the Concentration–Time Curve; CL: Clearance; RR: Relative Recovery; PK-PD: Pharmacokinetic-Pharmacodynamic; fT>MIC: Minimum Inhibitory Concentration for Bacterial Growth; MS: Median Sternotomy

Background

Children with congenital heart disease undergoing open cardiac procedures are a vulnerable population with reported surgical site infection (SSI) rates varying from 1.7 to 8.0 per 100 cases [1-5]. Multiple risk factors for development of an SSI have been identified in pediatric cardiac surgical populations, including intraoperative hypothermia and duration of surgery [1-5,6-11]. Cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) used during some pediatric cardiac surgeries have physiologic effects that alter drug disposition and pharmacokinetics (PK) [6,7]. In pediatric patients, these changes may be more pronounced and different than adults, given that the ratio of CPB priming volume to patient’s blood
Aeruginosa [1-5,8-10]. Staphylococcus aureus (MSSA), methicillin-resistant Staphylococcus aureus (MRSA), coagulase-negative staphylococci, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, and Pseudomonas aeruginosa [1-5,8-10].

A critical component of SSI prevention in cardiac surgery is the administration of prophylactic peri-operative antibiotics. For SSI prevention, effectiveness depends on selecting the appropriate antibiotic as well as timely administration to achieve effective plasma and tissue concentrations before skin incision, during the procedure, and in the immediate postoperative period [17]. Previously published pediatric pharmacokinetic studies investigating prophylactic antibiotics with CPB have used plasma concentrations as a surrogate for tissue drug concentrations [18-21]. Porcine models have been used routinely for Pharmacokinetic (PK)/Pharmacodynamic (PD) analysis [22]. Microdialysis (MD) is a method to directly sample interstitial fluid of tissue, and permits quantification of unbound drug concentrations in tissue [23-28]. Data on tissue penetration of antimicrobials into the surgical site, or tissue adjacent to the site, may result in modification of the current prophylactic antibiotic dosing recommendations.

The purpose of this study was to determine the plasma and tissue disposition of cefazolin, a first-generation cephalosporin commonly used for peri-operative antibiotic prophylaxis, in an immature porcine model of pediatric cardiac surgery and cardiopulmonary bypass.

Methods

Animal Model:

All protocols were reviewed and approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania, in compliance with the National Institutes of Health guidelines. Piglets (3-5 days old, female N=4/group, 2.1-2.7 kg) underwent induction and maintenance of anesthesia with isoflurane, fentanyl, and pancuronium. A tracheostomy was performed and femoral arterial and venous catheters were placed for blood pressure monitoring and blood sampling. Piglets received a median sternotomy (MS) or median sternotomy plus cardiopulmonary bypass with deep hypothermic circulatory arrest (CPB+DHCA). Piglets in the MS alone group were maintained at 37°C for the entire experiment and were subsequently euthanized with 4M KCl. The published protocol used for CPB+DHCA included cooling to 18°C over 30 minutes, DHCA for 30 minutes followed by 1 hour of low flow CPB (20 mL/kg/min), and finally rewarming over 30 minutes to 37°C [29]. Cefazolin dosing mimicked the clinical pathways currently in place at the Children’s Hospital of Philadelphia Cardiac Center.

Microdialysis method

Microdialysis (MD) utilizes the implantation of a small catheter with a semi-permeable membrane into tissue and can be used to obtain samples of interstitial fluid (IF) of the particular tissue of [26-28]. A physiological fluid is slowly perfused through the microdialysis catheter. Substances (analytes) present in the surrounding IF diffuse through the semipermeable membrane via a concentration gradient into the perfusion fluid and then the microdialysate fluid is collected and analyzed. It is a reliable, relatively low cost, and minimally invasive method used in clinical pharmacology to collect unbound drug in tissue IF [26-28].

Study Protocol

Two in vivo microdialysis (MD) catheters (CMA 20 Elite, Solva, Sweden) with a microdialysis membrane length of 10 mm and molecular weight cut-off of 20,000 Daltons were used in each subject. Under sterile conditions, one catheter was inserted under sterile conditions into the subcutaneous tissue and one catheter was inserted into the dorsal pectoralis muscle immediately adjacent to the sternum and future incision site. In vivo retrodialysis [26,28] was used to calibrate the microdialysis catheters. Briefly, cefazolin was diluted in 0.9% NaCl solution to a final concentration of 25 or 30 μg/mL (Cefazolin Concentrationperfusate) and perfused the microdialysis catheters at a rate of 1.5 μL/min. After an equilibration time of 30 minutes, microdialysate vials were changed and a dialysate sample was collected over 30 minutes. The concentrations of cefazolin were measured in the dialysate (Cefazolin Concentrationdialysate) to determine the relative recovery with the following equation [28]:

Relative Recovery (%)=100-(100* Cefazolin Concentrationdialysate/ Cefazolin Concentrationperfusate)

The microdialysis catheter as well as inflow and outflow tubing was flushed with 0.9% NaCl for 30 minutes and for the remainder of the experiments the microdialysate perfusion fluid was 0.9% NaCl at a flow rate of 1.5 μL/min.

After in vivo calibration and washout, piglets in both groups received intravenous cefazolin 25 mg/kg five minutes prior to incision.
Piglets that underwent CPB+DHCA received a second dose of 25 mg/kg of cefazolin added to the pump prime for a total dose of 50 mg/kg. At the time of this study, this antibiotic dosing protocol was standard of care for human children undergoing similar procedures at The Children’s Hospital of Philadelphia. Microdialysis samples from the subcutaneous and muscle catheters were collected continuously from the initial dose of cefazolin until the animal was separated from CPB and/or sacrificed and stored at -80°C until analysis. Blood samples were collected post-oxygenator via the extracorporeal circuit into lithium-heparin tubes, centrifuged, and plasma separated with storage at -80°C until analysis.

Figure 2: Semi-logarithmic concentration-time profile for total plasma, muscle, and subcutaneous tissue cefazolin concentrations over time for piglets that underwent median sternotomy (MS, n=4). The horizontal lines indicate various concentration targets and associated SSI pathogen(s). Abbreviations: μg: Microgram; mL: Milliliter; MSSA: Methicillin sensitive Staphylococcus aureus; E: Escherichia; K: Klebsiella; S: Staphylococcus; sp: Species.

Cefazolin Concentration Determination

Cefazolin concentrations in muscle and subcutaneous MD samples (unbound cefazolin concentrations) as well as plasma samples (total cefazolin concentrations) were determined utilizing a validated high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS) methodology at The Children’s Hospital of Philadelphia.

Plasma samples were prepared by adding 25 μL of an internal standard (5 mcg/mL ampicillin in water) to 25 μL of sample followed by 500 μL of cold methanol. The sample was vortexed for 1 minute, 450 μL of water was added, vortexed a second time and then centrifuged at 4000 rpm for 15 minutes. 100 μL of the supernatant was added to a microtiter plate followed by 900 μL of water prior to analysis. Microdialysate samples were loaded onto a microtiter plate in 10 μL volumes followed by 500 μL of the internal standard (20 ng/mL Ampicillin in water) prior to analysis.

Pharmacokinetic Analysis

Pharmacokinetic analyses were performed on cefazolin concentrations based on non-compartmental methodology. Maximum plasma concentration (Cmax) and time to maximum plasma concentration (Tmax) were determined. For piglets that underwent CPB+DHCA, Cmax1 and Tmax1 were identified after the first bolus and prior to initiation of CPB while Cmax2 and Tmax2 represent the concentration and time after the second bolus was administered on CPB. Area under the concentration - time curve (AUC) for plasma samples was calculated using the linear trapezoid method. Total clearance was calculated by dividing the total dose by the total AUC. Descriptive statistics were calculated for Cmax, Tmax, AUC and clearance (CL).

<table>
<thead>
<tr>
<th></th>
<th>Total Plasma</th>
<th>Muscle</th>
<th>Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS</td>
<td>CPB+DHCA</td>
<td>MS</td>
</tr>
<tr>
<td>AUC (μg/min mL-1)</td>
<td>5220.1 (4275.5-6487.1)</td>
<td>21844.1 (16527.4-26587.8)</td>
<td>3720.3 (3194.0-4212.1)</td>
</tr>
</tbody>
</table>

Figure 3: Box and whisker plots of median AUC ratios. Muscle AUC/total plasma AUC ratios for piglets that underwent CPB+DHCA (n=4) were significantly decreased compared to MS only (n=4) (*P=0.03). Subcutaneous AUC/total plasma AUC ratios for piglets that underwent CPB+DHCA (n=4) were significantly decreased compared to MS only (n=4) (**P=0.03).
The purpose of this study was to determine the plasma pharmacokinetics and tissue disposition of cefazolin in an immature porcine model of pediatric cardiac surgery and cardiopulmonary bypass.

We found that the maximal tissue concentrations of cefazolin were similar between piglets who underwent CPB+DHCA and who received twice the amount of cefazolin (total dose 50 mg/kg) compared to piglets that underwent MS alone (total dose 25 mg/kg).

Table 1: Pharmacokinetic parameters for cefazolin in piglets undergoing MS only (n=4) and CPB+DHCA (n=4).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MS only</th>
<th>CPB+DHCA</th>
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<tbody>
<tr>
<td>Cmax1 (μg/mL)</td>
<td>30.8 (23.5-42.6)</td>
<td>40.7 (36.7-47.8)</td>
</tr>
<tr>
<td>Tmax1 (min)</td>
<td>30 (30-30)</td>
<td>30 (30-30)</td>
</tr>
<tr>
<td>Cmax2 (μg/mL)</td>
<td>111.4 (88.3-122.5)</td>
<td>40.3 (41.8-56.8)</td>
</tr>
<tr>
<td>Tmax2 (min)</td>
<td>28 (22-34)</td>
<td>95 (15-176)</td>
</tr>
<tr>
<td>Total Clearan (L/hr)</td>
<td>0.7* (0.6-0.8)</td>
<td>0.3* (0.3-0.4)</td>
</tr>
</tbody>
</table>

Values displayed as medians (IQR). Cmax1 and Tmax1 are not reported for the MS group as they received only one dose of cefazolin. Total clearance is only able to be calculated from plasma samples so is not reported for the microdialysis samples. Significant p values reported below were calculated using the Wilcoxon rank sum test. Abbreviations: MS: Median Sternotomy; CPB+DHCA: Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest; AUC: Area under the Concentration-Time Curve; Cmax1: Maximum Concentration after Dose 1; Cmax2: Maximum Concentration after Dose 2; Tmax1: Time to Maximum Concentration after Dose 1; Tmax2: Time to Maximum Concentration after Dose 2; μg: Microgram; mL: Milliliter; min: Minutes; L: Liters; hr: Hour. * P = 0.03

Discussion

The pharmacokinetic-pharmacodynamic (PK-PD) factor most closely associated with cephalosporin antibacterial effectiveness is the amount of time the concentration of cephalosporin exceeds the relative recovery (RR) by the time interval of the microdialysis sample collection then summation of the areas for each interval. Interstitial concentrations for microdialysis samples were calculated using the following:

Interstitial Concentration = 100 × (concentration_dialed/f) / (concentration_vivo)

The median RR (IQR) was 33.5% (27.9-38.4%) for the subcutaneous microdialysis samples and 28.5% (20.6-42.2%) for the muscle samples, respectively.

Cefazolin penetration from plasma into tissue space was determined by calculating the ratio of tissue AUC (muscle and subcutaneous) divided by the total plasma AUC.

The pharmacokinetic-pharmacodynamic (PK-PD) factor most closely associated with cephalosporin antibacterial effectiveness is the amount of time the concentration of cephalosporin exceeds the minimum inhibitory concentration for bacterial growth (MIC) in the bloodstream or tissue in question [30]. For this reason, total plasma concentrations and measured unbound interstitial fluid concentrations of cefazolin in skeletal muscle and subcutaneous tissues were compared to the relevant MIC90 values31 and the duration of time above target concentrations was estimated based on visual inspection of the data. Summary data are reported as medians with interquartile ranges (IQR) with non-parametric comparisons, where appropriate. Statistical analyses and plots were completed using R, Microsoft Excel, or S-PLUS. In this pilot study, eight animals completed the protocol due to budgetary considerations.

Table: Pharmacokinetic parameters for cefazolin in piglets undergoing MS only (n=4) and CPB+DHCA (n=4).

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Citations:

Furthermore, peak cefazolin concentrations in the tissue samples were not seen until approximately 15-30 minutes after the bolus dose in both groups compared to within 5 minutes for the plasma samples.

### Table 2: Estimated percentage of time during surgical procedure cefazolin concentrations spent above different concentration targets.

<table>
<thead>
<tr>
<th>Target</th>
<th>SSI Pathogen</th>
<th>Total Plasma</th>
<th>Muscle</th>
<th>Subcutaneous</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>MS CPB+DHCA</td>
<td>MS CPB+DHCA</td>
<td>MS CPB+DHCA</td>
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<tr>
<td>2 μg/mL</td>
<td>MSSA</td>
<td>100% (97-100%)</td>
<td>100% (100-100%)</td>
<td>100% (100-100%)</td>
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<tr>
<td>16 μg/mL</td>
<td><em>E. coli K. pneumoniae</em></td>
<td>48% (28-76%)</td>
<td>100% (100-100%)</td>
<td>67% (60-73%)</td>
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<tr>
<td>32 μg/mL</td>
<td><em>S. epidermidis</em></td>
<td>31% (15-46%)</td>
<td>99% (98-100%)</td>
<td>26% (23-29%)</td>
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<td></td>
<td><em>Enterobacter sp.</em></td>
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</table>

Each concentration target represents an estimated MIC90 of bacteria [31] potentially susceptible to cefazolin and known to cause SSIs in pediatric cardiac surgical patients. Abbreviations: MS: Median Sternotomy; CPB+DHCA: Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest; μg: Microgram; mL: Milliliter; min: Minutes; MSSA: Methicillin Sensitive *Staphylococcus aureus*; E.: *Escherichia*; K.: *Klebsiella*; S.: *Staphylococcus*; sp.: Species.

For the CPB+DHCA group, total plasma levels peaked early and dropped precipitously following the first dose, which is likely a reflection of initial cefazolin distribution. Importantly, after the second bolus dose of cefazolin was given to this group, there was a lower Cmax2 compared to Cmax1, which is likely a reflection of the increased volume of distribution seen with the initiation of CPB. In addition, after the second bolus dose, the peak tissue concentrations appeared during or after rewarming from hypothermia and close to the end of CPB. This was seen despite twice the total dose of cefazolin being given to the CPB+DHCA group and that the total clearance of cefazolin resulted in relatively constant plasma concentrations during CPB+DHCA that then decreased again during rewarming and following separation from CPB, which was accompanied by an increase in the muscle and subcutaneous tissue concentrations of cefazolin. While microdialysis has many advantages for pharmacokinetic investigations, it must be noted that microdialysis samples lack the temporal discrimination of plasma samples. This is because drug concentrations measured in the microdialysis samples are average concentrations over the time interval collected and, therefore, cannot be analyzed as point estimates. To mitigate this effect in interpreting the data, relatively short time intervals of collection were used, microdialysis samples were paired with plasma samples where possible, and AUC comparisons were made, which inform about the overall exposure of skeletal muscle, subcutaneous tissue, and plasma to cefazolin, respectively.

The CPB+DHCA group had significantly lower AUCtotal ratios for both muscle/plasma and subcutaneous/plasma. This suggests that the combination of hypothermia and circulatory arrest impacts the ability for cefazolin to penetrate into tissue, possibly due to alterations in perfusion. This is supported by the observation that despite the decrease in plasma concentrations after rewarming and removal from CPB, tissue concentrations increased. Alternatively, in these experiments, it is unknown how hypothermia affects the relative recovery of the microdialysis membranes.

Cephalosporins are classified as time-dependent in their activity and the time above the MIC90 is important for their effectiveness [31]. Prophylactic antibiotic coverage during surgical procedures mainly targets skin flora (mainly gram-positive organisms) but in the SSI literature for pediatric cardiac surgical populations there is a significant proportion of SSIs that are caused by gram-negative pathogens [1-5,8-10]. There are no clear guidelines on what tissue concentrations should be targeted for prophylactic antibiotics, but targeting the MIC90 of organisms (see Methods section) seems reasonable. In these experiments, the dosing of antibiotics that was tested is likely adequate to cover MSSA (MIC90 2 μg/mL) [31], in both MS and CPB+DHCA groups, and may be adequate to cover organisms with MIC90 values close to 16 μg/mL, such as *Escherichia coli* and *Klebsiella pneumoniae* [32].

Given how CPB can alter drug pharmacokinetics and how quickly the plasma and tissue concentrations of cefazolin decrease in the MS group, a second dose of cefazolin in the bypass prime or given on initiation of CPB in pediatric populations appears to be prudent. This reinforces the conclusions that our group proposed in a recently published paper using similar methodologies in a human pediatric cardiac surgical population [33], and now provides a high-fidelity large animal model from which to test dose response and schedule that will inform translational pediatric studies for optimal dosing strategies. In addition, as tissue concentrations do not peak until approximately 15-30 minutes after the first bolus dose, the timing of cefazolin administration related to the initial surgical incision may be important to ensure adequate tissue concentrations at the time of incision, a time with high risk for potential contamination of the surgical wound. The timing of the first dose is critical for prophylaxis and this study gives some clinical direction for the exact timing of the first dose of prophylactic antibiotics in an immature animal. Future translational studies can now focus on this time period in high-risk pediatric populations. This delayed time of tissue distribution has also been demonstrated in adult populations and one pediatric population with peri-operative prophylactic antibiotic administration [33-37].
Limitations of this study include a small sample size and there is no ability to make any comments on post-operative cefazolin concentrations or pharmacokinetics. We did not estimate unbound cefazolin concentrations in plasma, as there exists no good estimate of protein binding of cefazolin in a porcine model. In humans, cefazolin does demonstrate concentration-dependent protein binding, with \( \text{in vivo} \) binding ranging from 85% at low concentrations to 52% at high concentrations [38]. In vivo studies in animal models have also shown concentration-dependent protein binding as well [39-41]. For this study, when we use the total plasma concentrations of cefazolin, there is a decrease in the estimated \( \frac{A}{M} \text{IC} \) with higher concentration targets in the MS only group (Table 2) that would only be exacerbated if protein-binding were known. This is potentially important clinically as the MS only group may be thought of as representing non-cardiac surgical procedures and warrants further investigation in other pediatric surgical populations.

Finally, the data presented here further demonstrate that CPB and DHCA significantly alter the plasma, muscle, and subcutaneous tissue pharmacokinetics of cefazolin. To date, except for one study [33] previously published pediatric pharmacokinetic studies investigating prophylactic antibiotics during CPB have used plasma concentrations as a surrogate for tissue drug concentrations [18-21], which may not provide adequate information to fully inform dosing strategies. This study provides further practical and conceptual knowledge for translation of these methods into pediatric populations so that objective data can be generated that will help guide peri-operative antibiotic dosing. One can foresee the application of minimally invasive methods and advances in pharmacokinetic-pharmacodynamic modeling that will help optimize drug delivery during extracorporeal support and various pathophysiologic states that could adapt to emerging pathogens and resistance in human children.

Conclusions

This large animal translational model provides the principles and foundations for further clinical investigation as proof of concept and safety for these high-risk pediatric patients to evaluate whether current cefazolin dosing recommendations achieve desired pharmacodynamic targets. Perhaps, even more importantly, these techniques will advance our understanding of how to individualize pharmacotherapy for patients with complex congenital heart disease undergoing surgical procedures.

References


