Cefazolin Tissue Penetration in a Porcine Model of Cardiac Surgery and Cardiopulmonary Bypass Measured by In Vivo Microdialysis

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ABSTRACT BODY:

Introduction: Surgical site infections (SSI) are the second most common cause of nosocomial infection. There is limited data in pediatrics, but surgical site infection rates may range from 2 to 12% of all pediatric cardiac surgical patients, despite current standard prophylactic antibiotics [1, 2]. Unfortunately, antibiotic dosing is guided by plasma concentrations and not by actual tissue penetration. We hypothesize that currently accepted cefazolin dosing guidelines do not adequately achieve tissue concentration above the mean inhibitory concentration (MIC_{90}) for common organisms causing surgical site infections in cardiac surgery; and, that by using in vivo microdialysis in a immature porcine model of cardiac surgery and cardiopulmonary bypass, knowledge can be gained to develop informed dosing guidance that will optimize tissue penetration and ultimately reduce the incidence of SSI.

Methods: Following IACUC approval, piglets (3-5 days old, female N=4/group) underwent median sternotomy (MS) or median sternotomy + cardiopulmonary bypass (MS + CPB). In vivo microdialysis was employed to measure unbound interstitial concentrations of cefazolin in subcutaneous tissue and muscle immediately adjacent to median sternotomy incision [3]. Each piglet received an intravenous dose of cefazoin (25 mg/kg) immediately prior to incision, and MS + CPB group received an additional dose of 25mg/kg (total 50 mg/kg) during initiation of CPB via priming volume. Plasma and dialysate concentrations were collected. Pharmacokinetic parameters, including Cmax and Tmax were identified. The area under the concentration time curve (AUC) was calculated using non-compartmental analysis .

Results: Median peak concentrations of 41.5 (ug/ml) in the muscle and 49.5 (ug/ml) in the subcutaneous space occurred at 15 and 30 min, respectively during MS. Median peak concentrations resulted in of 49 (ug/ml) in muscle and 44 (ug/ml) following initiation of CPB and the second dose of cefazolin during MS + CPB. There was no significant difference between the dose normalized (AUC/dose) AUC in muscle for pigs on CPB vs. those that underwent sternotomy alone (p=0.68). However dose normalized AUC in plasma was significantly higher in the CPB group (p=0.057).

Table 1 and 2: Pharmacokinetic parameters represented as Median (range) values

Table 1. Sternotomy (MS)	Plasma	Muscle	Subcutaneous
AUC (ug*min* ml^{-1})	2691 (2056,8501)	2629 (1789, 3585)	3501 (1836,4034)
Cmax (ug/ml)	154 (75, 179)	41.5 (32, 46)	49.5 (40, 59)
Tmax (min)	5	15 (15, 30)	30 (15, 30)

Table 2. MS + CPB	Plasma	Muscle	Subcutaneous
AUC (ug*min* ml^{-1})	20791 (14194,25024)	3994 (14194, 25024)	5222(4177,6429)
Cmax 1(ug/ml)	189 (132, 280)	26 (21, 47)	38 (31, 48)
Tmax 1(min)	5	30 (15, 30)	30 (15, 30)
Cmax 2(ug/ml)	111 (76, 130)	49 (21, 86)	44 (30, 59)
Tmax 2(min)	42.5 (30, 60)	52.5 (30,60)	45 (45, 60)

Discussion: The goal of prophylactic antibiotics is to achieve tissue concentrations exceeding the MIC_{90} of common bacteria that cause surgical site infections; gram positive organisms: *S epidermidis* and *S aureus*, and gram negative organisms: *Serratia sp* and *Enterobacter*. Current dosing recommendations in our model of porcine cardiovascular surgery resulted in plasma concentrations exceeding MIC_{90} for all organisms. **However, interstitial tissue concentrations (muscle/subcutaneous) did not exceed MIC_{90} for the gram negative organisms, *Enterobacter and Serratia* prior to incision or at ANY time over a four hour period during median sternotomy or CPB.** Furthermore, pigs that underwent MS + CPB received twice the amount of drug that pigs than MS alone, yet maximal tissue concentrations were similar in both groups. Despite the significantly larger plasma dose normalized AUC in the CPB group; pigs that underwent CPB did not achieve higher dose-normalized muscle AUCs. This suggests that either tissue becomes saturated and maximal tissue concentrations are achieved despite higher plasma exposures or that hypothermia associated with CPB impacts the ability for drug to penetrate into tissue. The latter is supported by an additional observation that despite the decrease in plasma concentrations after rewarming and removal from CPB, tissue concentrations increase This warrants further investigation in pediatric patients to better understand the impact of CPB and hypothermia on antibiotic disposition, specifically tissue penetration.

Refs.

1. Allpress, A.L., et al., Pediatr Infect Dis J, 2004. 23(3): p. 231-4.
2. Shah, S.S., et al., Thorac Cardiovasc Surg, 2007. 133(2): p. 435-40.
3. Hutschala, D., et al., Ann Thorac Surg, 2007. 84(5): p. 1605-10.