Pharmacodynamics of Antimicrobial Prophylaxis (AP) in Cardiac Surgery: Association Between Intraoperative Cefazolin (CFZ) Concentrations and Postoperative Infections

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BACKGROUND

- Surgical site infections (SSIs) are serious and potentially life-threatening complications following cardiac surgery.
- Although the principles of antimicrobial prophylaxis (AP) are founded on maintaining effective antimicrobial concentrations from incision to wound closure, studies that characterize antimicrobial activity in preventing SSIs are limited. In our previous study of AP in colorectal surgery, gentamicin plasma conc at wound closure was identified as one of the strongest independent risk factors for SSI.
- GOAL: To conduct a pharmacodynamic (PD) study of intraoperative cefazolin (CFZ) concs and postoperative infections in patients undergoing cardiac surgery with cardio pulmonary bypass (CPB).

METHODS

- A secondary PD analysis of AP in cardiac surgery was conducted using data from our pharmacokinetic study of CFZ during surgery. Inclusion criteria: adult patients undergoing elective cardiac surgery with CPB, no formal consent. SSIs within 30 days post surgery. Exclusion criteria: known or suspected infection or antimicrobials within 3 days of surgery, liver disease, Cl AB <50 mL/min/72 kg.
- AP was given via a peristaltic pump. CFZ 2 g was infused over 30 min pre incision, CPB during surgery and 48 h post surgery.
- Blood samples were collected 30 min after the dose peak (peak conc) prior to any repeat doses during surgery (time trough conc) and within 15 min of wound closure (closure conc). Whole blood samples were centrifuged to yield plasma and then re-centrifuged in a Centrifuge® device to yield protein-free ultrafiltrate. CFZ concs were determined by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) using LC-MS/MS as the internal standard. Assays were validated according to FDA Biophysical Analytical Methods guidelines on linear ranges of 4 to 100 mg/L (total conc) and 1 to 100 mg/L (free conc).
- Study subject characteristics and details regarding their surgery and CFZ prophylaxis were collected from medical records.
- Subjects were monitored for SSI during hospitalization using the CDC criteria. Subjects who consented were also contacted via phone for follow-up at 30 and 90 days post-surgery to identify clinically significant SSIs (i.e., requiring systemic antimicrobial therapy).
- Univariate analysis was used to examine potential subject-, surgery- and CFZ prophylaxis-related risk factors for SSI. Comparisons were made using two-tailed Student's t test, Mann Whitney U, or Fisher's exact test, as appropriate. Significant variables (P < 0.05) were included in multivariate logistic regression analysis (MVRUA) to assess their conditional significance for SSI following cardiac surgery.

RESULTS

- Forty (n = 40) study subjects were included in the PD analysis.
- Subject characteristics (LOS ± 1 day, BMI ± 1 kg) and details regarding surgery and CFZ prophylaxis are listed in Table 1: CABG, valve and mixed surgeries were conducted in 45% (18/40), 30% (12/40) and 25% (10/40) of cases, respectively. The mean duration of surgery was 241 ± 67 min. AP consisted of a preop CFZ dose only in 25% (10/40) of cases. The mean preop CFZ dose was 23.5 ± 4.5 mg/kg administered 38 ± 13 min prior to incision. The median CFZ closure conc was 86.5 ± mg/L ([95% CI 60.4–139.9 mg/L]) whereas the minimum conc (sweet conc during surgery including at wound closure) was 49.9 mg/L ([95% CI 34.5–52.1]).
- Eight (8) cases of superficial SSI of the sternal wound were identified.
- In univariate analysis (Table 1), depth, duration of CPB and surgery, CFZ closure conc and minimum conc were associated with SSI. The distribution of these variables in those with and without SSI is shown in Figure 1. In MVRUA (Table 2), duration of surgery (p = 0.027) and CFZ closure conc (p = 0.038) were independently associated with SSI. The probability of SSI based on the logistic regression model of CFZ closure conc and stratified for duration of surgery is depicted in Figure 2.
- Significant thresholds identified by Classification and Regression Tree (CART) analysis were duration of surgery > 346 min (SSI rate of 14.3% versus 60.0%) and CFZ closure conc > 1104 mg/L (SSI rate of 5% versus 30.4%).

CONCLUSIONS

- CFZ plasma concs at wound closure and duration of surgery were significant risk factors for SSI following cardiac surgery with CPB.
- CFZ closure concs was an important finding with its potential influence on the probability of SSI characterized by the logistic regression model shown in Fig 2.
- Minimum CFZ conc (lowest during surgery) was not a significant factor likely because intraop trough concs were soon followed by a repeat CFZ dose.
- The significance of total as opposed to free (active) CFZ concs in AP was an interesting finding that warrants further investigation.
- Small sample size was a limitation of the study that would have reduced the ability to identify other established risk factors for SSI such as age and diabetes.

Table 1: Univariate analysis factors associated with SSI following cardiac surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery</td>
<td>1.08</td>
<td>1.03–1.13</td>
<td>0.015</td>
</tr>
<tr>
<td>CFZ closure conc (mg/L)</td>
<td>1.00</td>
<td>1.00–1.01</td>
<td>0.490</td>
</tr>
<tr>
<td>CFZ minimum conc (mg/L)</td>
<td>1.00</td>
<td>0.98–1.02</td>
<td>0.714</td>
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</tbody>
</table>

Figure 1: Distribution of significant factors associated with SSI following cardiac surgery identified by univariate analysis

Table 2: MVRUA model of risk factors for SSI

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Figure 2: Probability of SSI vs cefazolin closure concs stratified for duration of cardiac surgery

REFERENCE:
- Zelenitsky SH, Grocott H, Arora R, Calic D. AAC 2002

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