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# Adequacy of Recommended Cefazolin (CFZ) Prophylaxis in Cardiac Surgery: A Prospective Pharmacokinetic (PK) Study

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## ABSTRACT

**BACKGROUND:** Although practice guidelines recommend the standard CFZ dosing for antimicrobial prophylaxis (AP) in cardiac surgery, there is limited study as to whether adequate concentrations (concs) are achieved in this population. The purpose of this PK study of CFZ AP in patients undergoing cardiac surgery was to determine the incidence of sub-therapeutic intra-op concs and to identify risk factors for failure to maintain target concs.

**METHODS:** The study was conducted with consent in adults undergoing cardiac surgery with cardiopulmonary bypass and receiving CFZ AP per institutional protocol (1 – 2 g IV pre-op based on body weight, repeated every 4 h during surgery). Blood samples were collected 30 min after the pre-op dose, prior to intra-op doses, and within 15 min of wound closure. A quantitative liquid chromatography-tandem mass spectrometry assay was developed to measure total CFZ concs. Based on pharmacodynamic (PD) principles for AP, the therapeutic target was defined as maintaining total CFZ concs ≥40 mg/L during surgery (≥ 8 mg/L free concs, assuming 80% protein binding).

**RESULTS:** Fifty-five subjects (69% male with a mean age of 65 ± 10 yrs, weight of 90 ± 17kg and Clcr of 80 ± 19 mL/min/72kg completed the study. Twelve (22%) subjects received 1 g CFZ doses and 43 (78%) were given 2 g doses. Total CFZ concs at closure (Cclosure) were <40 mg/L in 5 (9.8%) of the 51 evaluable cases, whereas levels below the target were observed at some point during surgery in 30.9% (17/55). A sub-therapeutic Cclosure was more frequently observed with 1 g doses for CFZ (p = 0.009), most commonly used in females (p = 0.001) and those with increased age (p = 0.037) and lower body weight (60 – 76kg, p < 0.001). Further analysis identified a critical dose threshold of > 24 mg/kg for maintaining target CFZ conc during surgery (p = 0.035).

**CONCLUSIONS:** Under current dosing guidelines sub-therapeutic CFZ concs occur frequently during cardiac surgery. As antimicrobial concs at wound closure are a risk factor for surgical site infections, current dosing guidelines may not be adequate. In addition, we demonstrate how PK-PD directed targets might be used to optimize AP and thus potentially reduce post-op infections.

## BACKGROUND

- Clinical practice guidelines recommend standard CFZ dosing (1 – 3 g q4h during surgery) for antimicrobial prophylaxis (AP) in cardiac surgery. (Bratzler 2013)
- To date, no studies have evaluated the currently recommended CFZ regimen to determine if targets are being achieved.
- Goal: To determine the incidence and risk factors for below-target CFZ concs at wound closure (<40 mg/L) with the recommended CFZ regimen in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

## METHODS

- Inclusion criteria: adult patients undergoing elective cardiac surgery with CPB and receiving CFZ prophylaxis
- Exclusion criteria: received >1 pre-op CFZ dose, known/suspected infection or antimicrobial use within 3 days of surgery, chronic liver disease, creatinine clearance (Clcr) <50 mL/min/72 kg
- AP was administered as per institution protocol (CFZ 1 or 2 g pre-op, q4h during surgery, and q8h for 48 hours after surgery).
- Blood samples were collected at 30 min after the pre-op dose (peak), prior to any intra-op dose (intra-op trough) and within 15 min of wound closure (closure conc).
- Whole blood samples were centrifuged at 1300 x g for 10 min to separate plasma.
- Total CFZ plasma concs were determined by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) using Shimadzu Nexara ultra-high performance liquid chromatograph and 8040 triple quadrupole mass spectrometer and an Acquity UPLC BEH C18 1.7 µm column.
- A stable isotope, $^{13}C_2{}^{15}N$ cefazolin (Toronto Research Chemicals), was used as the internal standard.
- CFZ assay was validated according to FDA Bioanalytical Methods [2001] for a linear range from 4 to 100 mg/L.
- Patient (gender, age, height, weight, Clcr, smoking status, surgical history, co-morbidities, medications, lab data), surgery (type, number and type of graphs if applicable, timing of incision, timing of CPB, timing of wound closure, fluid balance) and CFZ prophylaxis (doses, timing) data were collected from medical records.
- A target to maintain total CFZ concs ≥40 mg/L during surgery (free concs ≥8 mg/L, assuming 80% protein binding) was selected based on the epidemiology of pathogens in cardiac surgical site infections (Sievert 2013) and MICs of these pathogens in surgical patients in Canadian hospitals. (CANWARD)
- Potential risk factors for below-target CFZ closure concs of <40 mg/L were tested using univariate analysis, including Student's t-test, Pearson's Chi-square test or Fisher's exact test, as appropriate. Multivariate analysis was conducted with significant variables (p <0.1) using a backward, stepwise approach in a binary logistic regression model

## RESULTS

- 55 patients (mean age of 65 ± 10 years, body weight of 90 ± 17 kg, Clcr of 80 ± 19 mL/min/72 kg) completed the study. **(Table 1)**
- 26 patients (47.3%) underwent coronary artery bypass graft (CABG) surgery whereas 14 (25.5%) had valve replacement surgery **(Table 2)**; the mean duration of surgery was 258 ± 99 min.
- 43 patients (78.2%) received 2 g CFZ doses, while 12 patients (21.8%) received 1 g CFZ doses (selected in patients < 80 kg).
- 42 patients (76.4%) received a pre-op and at least one additional intra-op CFZ dose. **(Table 3)**
- 134 blood samples were collected including 53 peaks (136.7 mg/L, IQR 115.6 – 171.9 mg/L), 30 intra-op troughs (46.7 mg/L, IQR 35.7 – 52.4 mg/L) and 51 closure concs (89.4 mg/L, IQR 55.3 – 140.9 mg/L).
- 9.8% (5/51) of closure concs were <40 mg/L **(Fig 1)**, whereas 30.9% (17/55) of patients had a CFZ conc (i.e., intra-op trough or closure conc) <40 mg/L at some time during surgery **(Fig 1 and 2)**.
- In univariate analysis, female gender (p = 0.04), lower body weight (p = 0.02), valve surgery (p = 0.01), 1 g pre-op CFZ dose (p = 0.01) and lower total CFZ dose during surgery (p = 0.01) were significantly associated with CFZ closure concs <40 mg/L . **(Table 4)**
- Only the use of 1 g CFZ doses was independently associated with CFZ closure concs <40 mg/L (p = 0.013; OR = 0.053, $CI_{95\%}$ 0.005 to 0.536).

## CONCLUSIONS

- ✓ In 90% of patients, CFZ closure concs were above the target of ≥40 mg/L.
- ✓ However, 31% of patients had a CFZ conc below-target at some time during surgery.
- ✓ The use of 1 g CFZ doses was associated with below-target closure concs and should be avoided in patients undergoing cardiac surgery.

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### Table 1: Patient characteristics (n=55)

| | |
|---|---|
| Female | 17 (31%) |
| Age (years) | 65 ± 10 |
| Weight (kg) | 90 ± 17 |
| BMI (kg/m$^2$) | 30.9 ± 5.3 |
| Clcr (mL/min/72 kg) | 80 ± 19 |
| Co-morbidities | |
| Hypertension | 40 (73%) |
| Ischemic heart disease | 34 (62%) |
| Diabetes mellitus | 16 (29%) |
| Myocardial infarction | 11 (20%) |
| Charlson co-morbidity index | 3.0 ± 1.6 |
| Smoker (current / past) | 8 (15%) / 26 (47%) |
| Previous cardiac surgery | 2 (4%) |

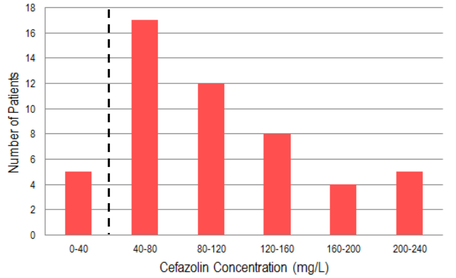
### Table 2: Surgery characteristics (n=55)

| | |
|---|---|
| CABG surgery | 26 (47%) |
| Valve surgery | 14 (26%) |
| Procedures with grafts (*n = 38*) | |
| Internal mammary artery | 28 (74%) |
| Saphenous vein | 31 (82%) |
| Number of grafts | 2.7 ± 1.3 |
| Fluids intra-op (mL) | 3547 ± 1301 |
| Blood products intra-op (mL) (*n = 17*) | 1944 ± 2107 |
| Duration of CPB (min) | 129 ± 78 |
| Duration of surgery (min) | 258 ± 99 |
| Intra-operative complications | 3 (6%) |
| Re-exploration | 5 (9%) |

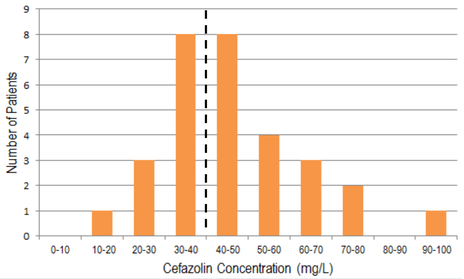
### Table 3: CFZ prophylaxis characteristics (n=55)

| | |
|---|---|
| 2 g CFZ dose | 43 (78%) |
| Pre-op CFZ dose (mg/kg) | 23.5 ± 5.1 |
| Total pre-op and intra-op CFZ dose (mg/kg) | 43.5 ± 16.7 |
| Total pre-op and intra-op CFZ dose (mg/kg/h) | 9.0 ± 2.4 |
| Number of CFZ doses | |
| Pre-op dose only | 13 (24%) |
| Pre-op dose plus 1 intra-op dose | 37 (67%) |
| Pre-op dose plus ≥ 2 intra-op doses | 5 (9%) |
| Timing of pre-op CFZ dose (min) | 35 ± 14 |
| ≤60 min before incision | 52 (95%) |
| Timing of CFZ re-dosing during surgery (*n = 48*) | 232 ± 15 |
| ≤4 h after previous dose | 44 (92%) |

### Fig 1: CFZ closure concs (n=51)




### Fig 2: CFZ intra-op trough concs (n=30)




### Table 4: Variables associated with below-target CFZ closure concs

| Variable | CFZ Closure Conc | | p-value |
|---|---|---|---|
| | <40 mg/L (*n = 5*) | ≥40 mg/L (*n = 46*) | |
| Female | 4 (80%) | 13 (28%) | **0.04** |
| Age (years) | 68.4 ± 9.5 | 64.8 ± 9.9 | 0.44 |
| Weight (kg) | 73.1 ± 6.1 | 91.3 ± 16.9 | **0.02** |
| Clcr (mL/min/72 kg) | 82.6 ±25.9 | 79.9 ± 18.2 | 0.76 |
| CABG surgery | 1 (20%) | 24 (52%) | 0.35 |
| Valve surgery | 4 (80%) | 9 (20%) | **0.01** |
| Duration surgery (min) | 191 ± 15 | 260 ± 84 | 0.08 |
| 1 g CFZ dose | 4 (80%) | 8 (17%) | **0.01** |
| Pre-op CFZ dose (mg/kg) | 19.0 ± 8.1 | 23.9 ± 4.8 | 0.05 |
| Total CFZ dose (mg/kg) | 24.8 ± 7.9 | 44.0 ± 15.3 | **0.01** |
| Total CFZ dose (mg/kg/h) | 6.6 ± 1.9 | 9.0 ± 2.2 | **0.02** |