#A007

Dose Optimization of Cefazolin in Adult Cardiac Surgery with Cardiopulmonary Bypass After Albumin Supplementation

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BACKGROUND

- Infections after cardiac surgery occurs in 0.5 to 7.8% of the patients, leading to increased risk of morbidity/mortality
- Cefazolin (CFZ) prevents such infections, and the efficacy is driven by the time which the unbound drug concentration is above the minimum inhibitory concentration (fT>MIC)
- Cardiac surgery with cardiopulmonary bypass (CPB) may require albumin supplementation, which is thought to alter unbound cefazolin concentrations

This study aimed to evaluate how albumin supplementation affects CFZ PK in cardiac surgery patients and the need for dose adjustments. Ultimately, this study aimed to evaluate the best dosing regimen for this cardiac surgery under this clinical conditions

METHODS

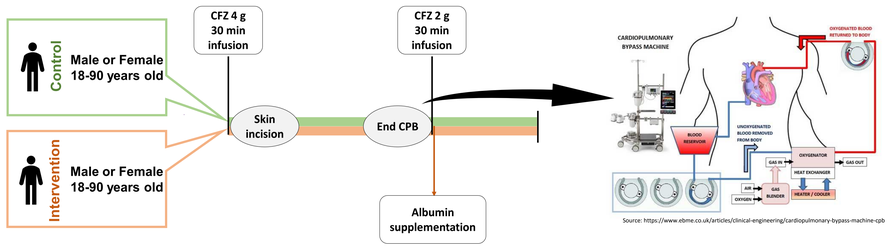


Figure 1. Clinical Trial protocol of CFZ IV in control and intervention patients, the later receiving albumin supplementation. CPB machine and scheme. CFZ: cefazolin; CPB: cardiopulmonary bypass.

- All patients (N=17) received 6g of CFZ, being the first dose of 4g 30 min before skin incision and the second dose of 2g after termination of CPB
- Total and unbound plasma concentrations were collected after CFZ first dose
- The unbound concentrations were collected through the microdialysis (MD) technique.

		Sampling times (minutes) CFZ first dose at T = 0								
Samples	Plasma	- 15	30	60	90	120	240	360	480	600
	MD		0-30	30-60	60-90	90-120	120-240	240-360	360-480	480-600

- A nonlinear mixed-effect modeling approach was used in NONMEM (version 7.4.4) to develop a PK model
- The probability of target attainment (PTA) against *Staphylococcus aureus* was predicted (= proportion of time which the unbound CFZ concentration is above the target concentration of 4 x MIC values)

RESULTS

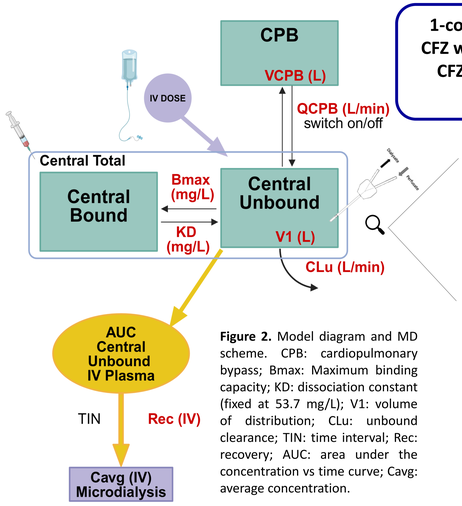


Figure 2. Model diagram and MD scheme. CPB: cardiopulmonary bypass; Bmax: Maximum binding capacity; KD: dissociation constant (fixed at 53.7 mg/L); V1: volume of distribution; CLu: unbound clearance; TIN: time interval; Rec: recovery; AUC: area under the concentration vs time curve; Cavg: average concentration.

1-compartment of distribution for unbound CFZ with first-order elimination, with a bound CFZ compartment, a compartment for the bypass, and prediction of recovery.

Table 1. Population PK model parameters

Parameter [units]	Population Estimates [% RSE]	Bootstrap analysis Median [95% CI]
Fixed effects and covariates (θ)		
CL [L/h]	11.8 [9.4]	11.9 [8.5, 15.7]
V1 [L]	40.9 [3.8]	41.3 [30.1, 54.8]
Bmax [mg/L]	210 FIX	[FIX]
Recovery [%]	40.4 [8.4]	40.6 [34, 47.7]
ALB_Bmax	0.571 FIX	[FIX]
Sex_V1	0.539 [23]	0.542 [0.413, 0.745]
Sex_CL	0.526 [26.2]	0.52 [0.374, 0.746]
Random effects (ω^2)		
CL	0.191 [28.8]	0.181 [0.07, 0.292]
V1	0.125 [40.3]	0.115 [0.038, 0.215
Recovery	0.068 [42.8]	0.064 [0.018, 0.131]
Covariance CL;V1	0.135 [32.7]	0.126 [0.031, 0.217]
Residual errors (ε)		
Prop Unbound	0.098 [13.8]	0.094 [0.072, 0.125]
Prop Total	0.051 [19.7]	0.049 [0.034, 0.07]

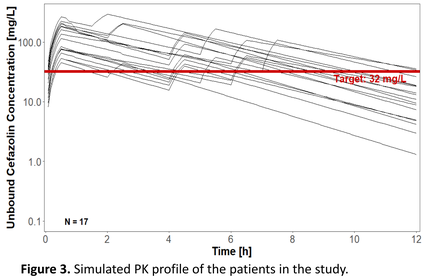
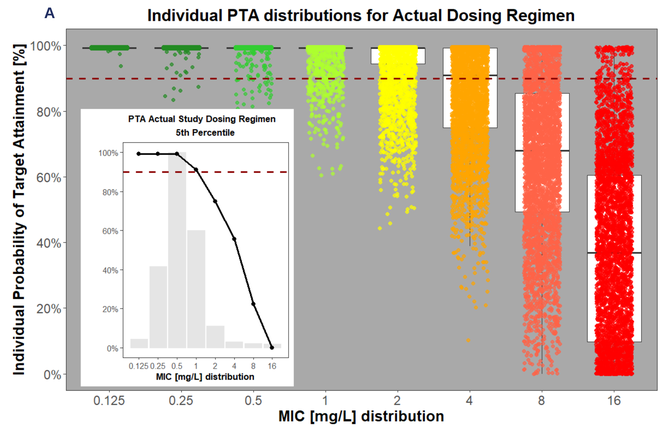


Figure 3. Simulated PK profile of the patients in the study.

A PTA above 90% could not be maintained for MIC equal to 2 mg/L or greater with the actual dosing regimen. A continuous infusion of 7.5 mg/min after 1.5g IV bolus loading dose achieves the targeted PTA for MIC up to 4 mg/L for at least 95 % of patients.



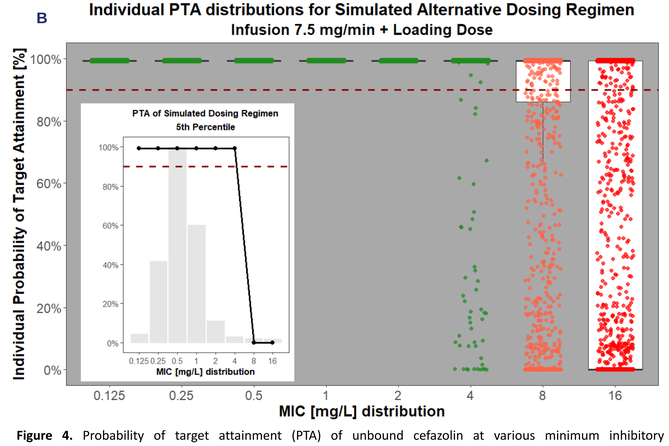


Figure 4. Probability of target attainment (PTA) of unbound cefazolin at various minimum inhibitory concentrations (MIC). A: PTA for a simulated dataset (N=4000) with the dosing regimen from the study. B: PTA for a simulated dataset (N = 4000) with continuous infusion of 7.5 mg/min after 1.5g of loading dose (IV bolus).

CONCLUSIONS

- The dosing regimen used in this study (two 30-minute infusions) is insufficient to cover the full MIC distribution of the pathogen of interest.
- Despite a moderate increase in the maximum binding capacity in the patients receiving albumin supplementation, the PTA does not differ between the two groups.
- A continuous infusion at a lower rate following a loading bolus dose is a better alternative.

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