Population pharmacokinetics of cefazolin in children undergoing elective cardiac surgery

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Background and Objectives

- Cefazolin is an antibiotic used as prophylaxis during surgical operations.
- For its efficacy, perioperative plasma concentrations need to be maintained above target [1].
- The objective of this study is to **describe the pharmacokinetics of cefazolin in small children** during cardiac surgery, characterizing in particular the **effect of the cardiopulmonary bypass (CPB), with or without the use of a priming dose.**

Methods

Data:

- observational study
- 22 children undergoing cardiac surgery requiring CPB (Table 1)
- cefazolin 50 mg/kg was administered IV before the surgery and then every 4 to 6 hours.
- For 7 children, a further dose of cefazolin was added to the priming volume of the CPB circuit.
- 10 to 15 blood samples per patient

Model building:

- NONMEM 7.2 (FOCE-I),
- Pirana,
- PSN,
- Xpose

Table 1 Patient info:

covariate	median	range
Age (months)	19.5	1.0 – 94.0
Weight (kg)	8.7	2.0 – 21.6
Height (gm)	77.5	45.0 – 117.0
CPB Priming Vol (mL/kg)	41.9	16.2 – 225.0
Time on CPB (min)	115	35 – 336

Results

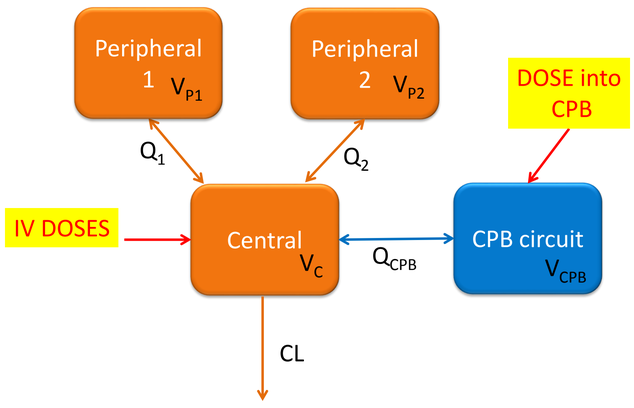

Figure 1 Structure of the final model

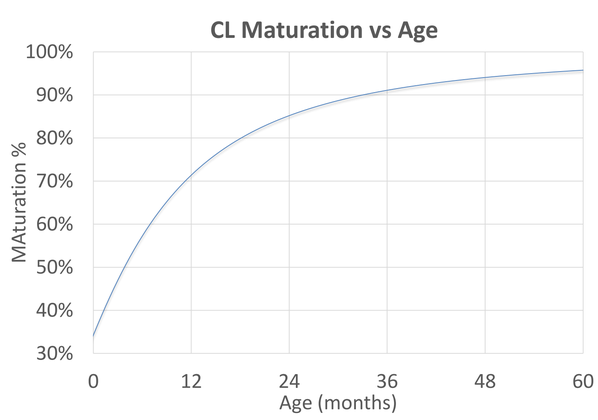

Figure 2 Clearance maturation

A **3-compartment model** with first-order elimination fit the data best (Figure 1).

The effect of the **CPB circuit during the surgery** was modelled as a separate compartment, connected and disconnected from the rest of the model at the recorded times. **Flow (Q_{CPB}) fixed to cardiac output** (plasma, 185 L/h for a 70 kg adult).

The **volume of the CPB compartment was proportional to the priming volume**.

All clearance and volume parameters were adjusted by body size using **allometric scaling** [2].

Clearance was found to mature with post-menstrual age [2]. The estimate of mature clearance for a 9 kg child was 0.8 L/h, with children born at term having 35% of this value and reaching 70% by 1 year of age (Figure 2).

Use of creatinine CL (in addition or instead) did not improve the model.

Table 2 Final parameter estimates (5th and 95th percentile)*:

Parameter	Typical Value	BSV+ or BOV++
CL[a] [L/h]	0.801 (0.598, 0.967)	8.3%+ (0.1%, 18.4%)
V_C [L]	0.901 (0.331, 0.961)	15.5%+ (0.2%, 24.0%)
Q_1 [L/h]	0.431 (0.261, 0.801)	
V_{P1} [L]	1.57 (0.651, 4.97)	
Q_2 [L/h]	1.61 (1.11, 6.31)	
V_{P2} [L]	0.691 (0.521, 1.05)	
Scaling V_{CPB} []	0.671 (0.451, 0.891)	
BIO []	1 FIXED	20.2%++ (14.1%, 24.7%)
PMAGE_50 [months]	13.1 (10.1, 20.1)	
Gamma []	1.91 (1.01, 9.91)	
Prop err [%]	13.7% (11.8%, 15.1%)	

All CL and V parameters reported for a 8.7 kg child, *Estimated from nonparametric bootstrap (n=150) of the final model
[a]This is the value of CL at maturity

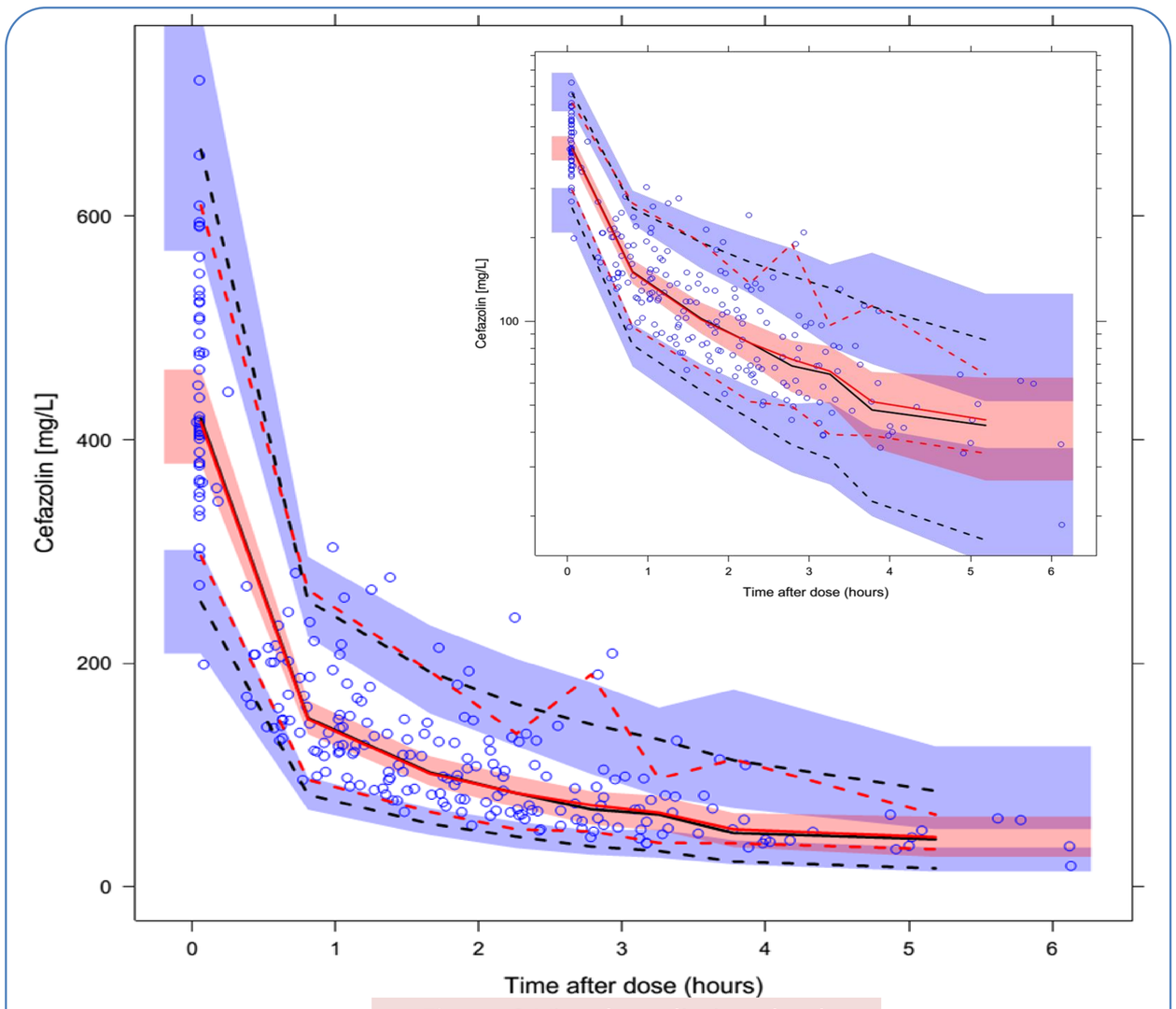

Figure 3 Visual predictive check

The whole dataset was re-simulated 1000 times to elucidate the effect of priming the CPB with an extra dose.

Standardised timings were used for sternal incision (0h30), CPB full flow (1h30), removal of CPB (3h30), extra dose (4h00), sternal closure (4h30).

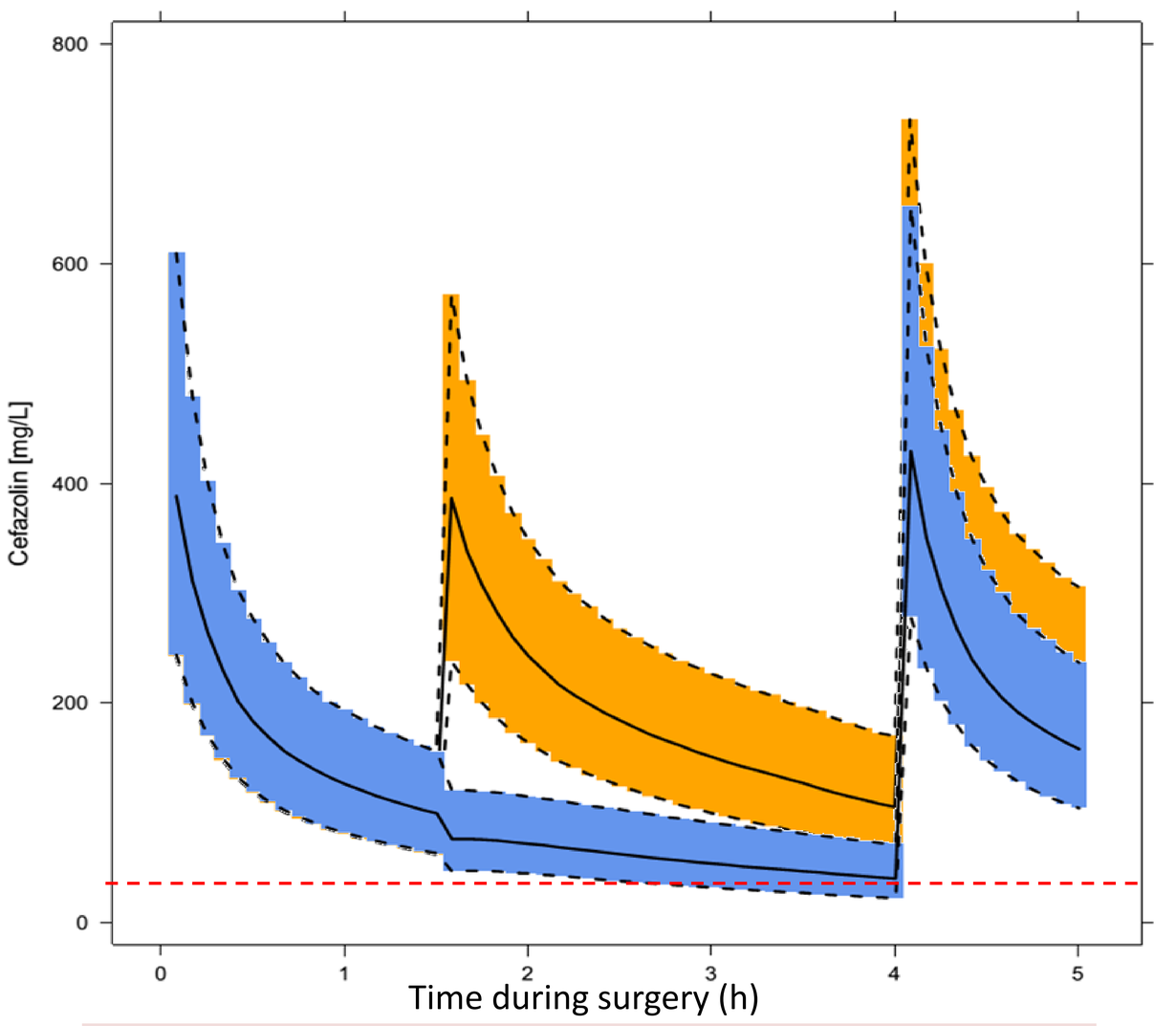

Figure 4 Simulated PK with (orange) and without (blue) CPB priming dose. Solid lines are median, dashed lines are the 5th and 95th percentiles. Red dashed line is 32 ug/mL, MIC_{90} for Staph. Aureus

Conclusions

The pharmacokinetics of cefazolin in children undergoing CPB surgery was described and the main sources of variability identified in **body weight and age.**

The model correctly predicted increasing concentrations when connecting a CPB circuit primed with an extra dose, and vice-versa.

The model predicts the **lowest concentrations following the connection of a CPB not primed** with extra cefazolin. Priming has a similar effect to that of an extra dose.

The model can inform dosing strategy, strength and frequency, by adjusting for body weight and age, particularly for very small or pre-term babies.

References

[1] F. H. Edwards, R. M. Engelman, P. Houck, D. M. Shahian, and C. R. Bridges, "The Society of Thoracic Surgeons Practice Guideline Series: Antibiotic Prophylaxis in Cardiac Surgery, Part I: Duration.," Ann. Thorac. Surg., vol. 81, no. 1, pp. 397–404, Jan. 2006.
[2] N. Holford, Y. Heo, and B. Anderson, "A pharmacokinetic standard for babies and adults.," J. Pharm. Sci., pp. 1–12, May 2013.