Evaluating New Dosing Strategies for the Use of Cefuroxime in Perioperative Antibiotic Prophylaxis using PBPK

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Introduction

The optimal dose and schedule of the perioperative antibiotic prophylaxis (PAP) is a matter of debate. Despite existing guidelines and recommendations, there are important issues of uncertainty regarding the timing and dose before incision and the intraoperative follow-up administrations. Another issue is the tissue penetration of the antibiotics used for PAP. Therefore, we collected perioperative plasma and tissue samples from 25 patients receiving cefuroxime. We developed a PbPk model in order to address the question of sufficient tissue concentrations.To evaluate effects on the pharmacokinetic (PK) triggered by the alteration of physiological conditions during surgery, we tested relevant changes using our model [1].

Conclusions

Our results show that the kinetic of Cefuroxime is influenced by age and kidney status (not by gender, BMI or the surgery [1]). The use of cefuroxime for perioperative prophylaxis to prevent Staphylococcal surgical site infections, seems to be reasonable and recommendable. According to our data the use of cefuroxime for perioperative prophylaxis in abdominal surgeries, using the described dosing regime appears to be at least questionable (Fig. a,c,f). With our dose recommendations we provide a solution for this issue.

Patients and Methods

Parameter	Mean (±standard deviation)
Age [years]	54.8 ± 14.9
Weight [kg]	82.7 ± 19.0
Height [cm]	175.1 ± 8.7
Male [%]	68
Albumin [g/dL]	3.7 ± 0.2
Creatinine clearance [ml/min]	105.6 ± 33.4
Fraction unbound of Cefuroxime estimated for every individual [%]	0.71 ± 0.01

Table 1: patient characteristics; N = 25 Patients thorax surgery; 135 plasma- / 20 lung-tissue-concentrations were collected, administered dose 1.5 g bolus every 2.5h

Software:
- PK-Sim®/MoBi® [2]; R (version 3.4.0)
  → Generic model for healthy adults

Adjustments:
- Consideration of changing ratio between glomerular filtration and tubular secretion
  → Establishment of a generic function to predict individual Clearance
- Consideration of low albumin concentrations using equation (1) of McNamara et.al [3]

Definition for antibiotic effectivity (Drusano [4]):
- Bacteriostatic = T > MIC 40%
- Bactericidal = T > MIC 70% of the dosing interval
- MIC = 2 mg/L and 8 mg/L for Staph. aureus and E.coli (EUCAST)
- Beta – Lactam drug concentration should exceed the MIC 4-6 times → 8 mg/L and 32 mg/L

Tissue re-evaluation:
- Feathering method
- Equation (2) Derendorf et al. [5]

$$C_{T(u)} = \frac{(a*\beta + b*\alpha)*(1-f_b)}{\beta-\alpha} * (e^{-\alpha*t} - e^{-\beta*t})$$

Equation 2: $C_{T(u)}$ = Concentration unbound peripheral compartment; a,b,α,β = hybrid constants describing an two-compartment-model with linear Kinetics; f_b = fraction bound, t =Time

Determination of tissue concentrations

$$[Drug] = \frac{\left(\frac{[Drug]_t * V * 100}{R} - B\right) * \rho}{m * \left(\frac{100}{100-T}\right)}$$

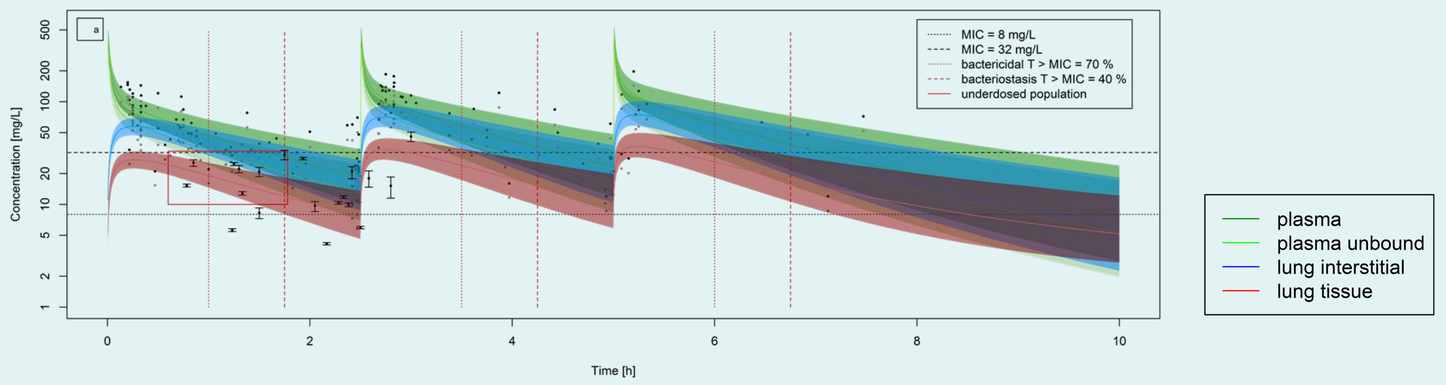
$$B = \frac{[Hb-tissue]_f * \left(1-\frac{Hkt}{100}\right) * [Drug]_P * m * \left(\frac{100}{100-T}\right)}{[Hb-blood]*10}$$

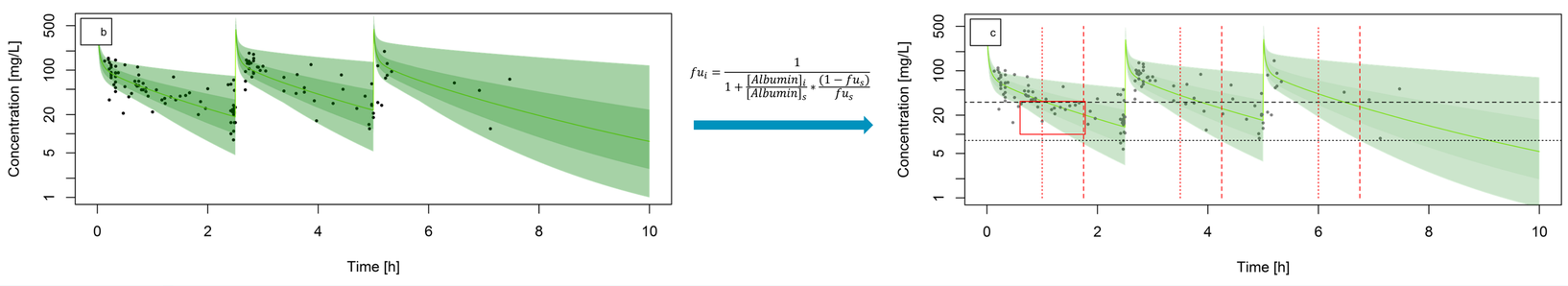
[Drug] = Drug concentration in tissue with out blood contamination [mg/L]; $[Drug]_t$ = Drug concentration in dried and homogenized tissue [mg/L]; V = Volume of the eluent [mL]; R = Recovery [%]; P = density [g/mL]; m = mass of weighted dried homogenized tissue [g]; T = drying loss (lost water content [%]); B = blood contamination; $[Hb-tissue]_f$ = Hemoglobin concentration in wet tissue [µg/mg tissue]; [Hb – blood] = Hemoglobin concentration during the time of tissue extraction [g/dL] Hkt = Hematocrit during tissue extraction [%]; $[Drug]_P$ = Drug concentration during tissue extraction [mg/L]

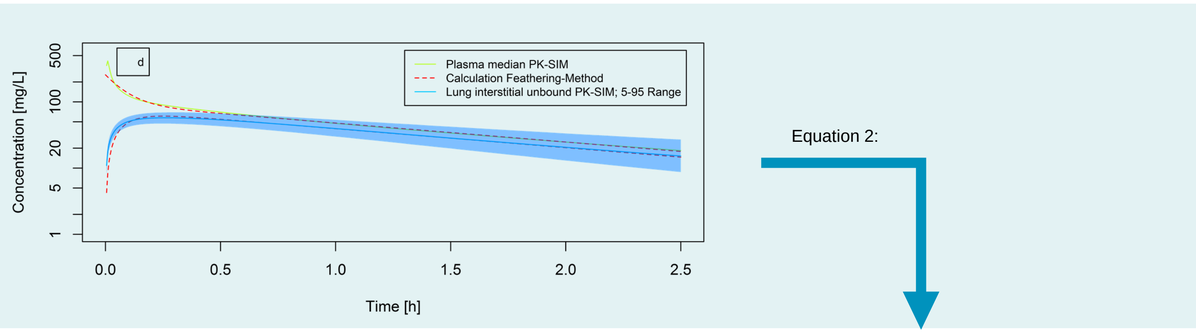
- Scale-up from the fitted tissue concentrations to interstitial concentrations
- fitted → lung endothelial permeability $2*10^{-5}$ cm/min

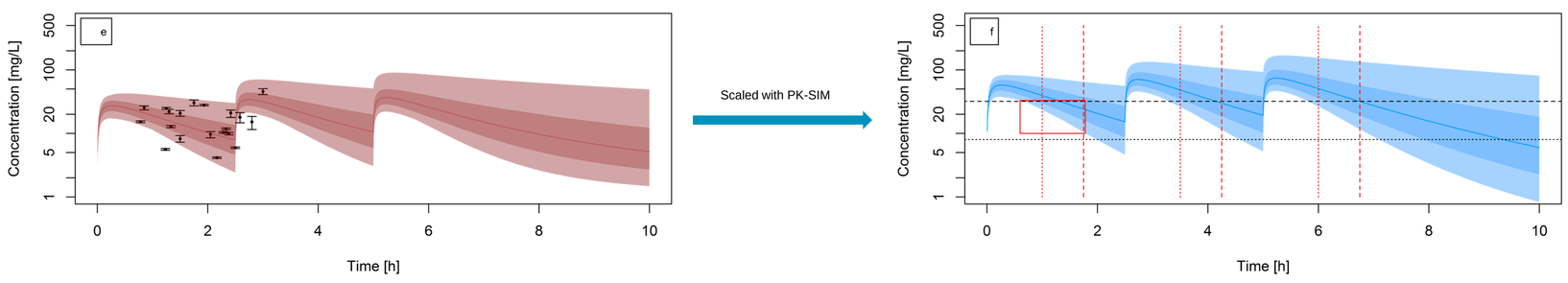
Tested Dosing regimes:
- Populations were splitted into three groups according the kidney function
- The slightly lower interstitial concentrations were used for dose recommendation, instead of the lung interstitial unbound concentrations
- Different dosing strategies were tested, with an maximum intraoperative dose of 3x1.5 g
- The two most promising dosing regimes were 1.5 g bolus every 2.5 h and 1.5 g bolus plus infusion with 3 g for 3 h

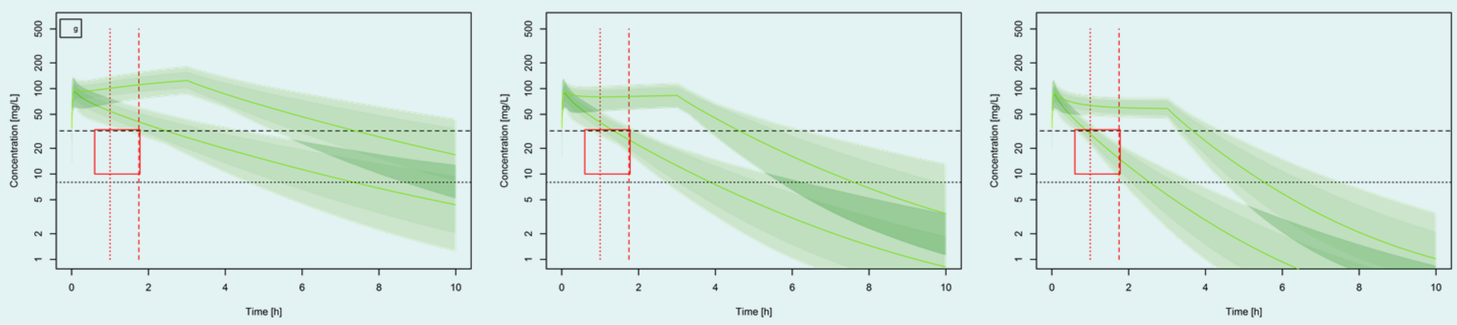
Results I









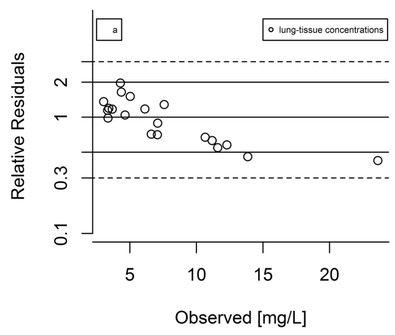


a = measured plasma- and tissue concentrations with simulated population curves; b = simulated plasma concentrations with measured plasma concentrations; c = simulated plasma unbound concentrations with calculated plasma unbound values; d = comparing PK-SIM simulation of lung interstitial unbound with the results from the feathering calculation and the equation 2 using R; e = simulated lung tissue concentrations with measured tissue concentrations; f = simulated lung interstitial population curves; g = first: GFR 40-80 mL/min, second: GFR 80-120 mL/min third plot: GFR 120-160 mL/min with administered doses of 1.5 g and 1.5 g bolus plus 3g as an 3 hour infusion; General: middle line = population median, darker area = 5 – 95 Range of population, brighter area = min. – 5 % and 95 % – max. of the population;

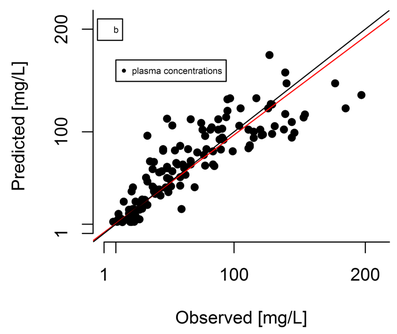
Results II

Model	MPE	MAPE
Literature	27.7	36.2
Renal adjusted	12.2	29,8
Individual f_u (preoperative)	5.4	27.3
Physiological changes	- 4.6	29.3
Total Cefuroxime clearance		
- 5 %	-1.7	29.0
- 10 %	1.4	29.0
- 20 %	8.4	29.5
Population	10.4	27.3

Table 1: Prediction errors for the individual calculations; MPE = mean prediction error; MAPE = mean absolute prediction error



a = relative residuals for lung tissue concentrations,



b = goodness-of-fit plot for the measured plasma concentrations

Kidney function		bolus 1.5 g bacteriostatic	bolus 1.5 g bactericidal	1.5 g bolus 3 h Infusion 3 g bacteriostatic	1.5 g bolus 3 h Infusion 3 g bactericidal
improved	MIC 32 mg/L	1.5	0.8	8.1	4.6
	MIC 8 mg/L	4.6	2.6	11.1	6.4
normal	MIC 32 mg/L	1.8	1.0	9.5	5.4
	MIC 8 mg/L	6.7	3.8	14.2	8.1
low	MIC 32 mg/L	3.4	1.9	13.1	7.5
	MIC 8 mg/L	11.4	6.5	21.6	12.3

Table 2: Dose recommendation; 32 mg/L against E.coli; 8 mg/L against Staph. aureus; bacteriostatic = T > MIC 40% and bactericidal = T > MIC 70% of the dosing interval; results in [h] of protection [4]; improved = 120-160 , normal = 80-120 low = 40-80 mL/min eGFR

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