Development of a PBPK Model to Predict the Tissue Concentrations of Cefuroxime During Surgery

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Introduction

The goal of this study is to predict the plasma and tissue concentrations of the cephalosporine antibiotic cefuroxime during surgery. In order to develop an adequate dose recommendation for the perioperative antibiotic prophylaxes, we included relevant changes in physiology during surgery, which may affect the pharmacokinetics of administered drugs. For this purpose, we developed and evaluated a physiologically-based pharmacokinetic (PBPK) model, using PK-Sim®/MoBi® [1].

Patients and Methods:

Software:
– PK-Sim®/MoBi®
Basis:
– Generic literature model for healthy adults
Adjustments:
– Consideration of changing ratio between glomerular filtration and tubular secretion
  → Establishment of a generic function to predict individual clearance
– Re-evaluation with samples from 10 patients
– Consideration of low albumin concentrations using equation 1 (McNamara et.al [2]).
– Inclusion of parameters influencing the pharmacokinetics (Pk) during surgery (Figure 1)
– Corrections of endothelial permeability to describe tissue concentrations
Population simulations:
– scale-up from the fitted tissue concentrations to interstitial concentrations
Tissue re-evaluation:
– feathering method
– equation Derendorf et al. [3]

Variable	Thorax Mean (±standard deviation)	hand surgery re-evaluation Mean (±standard deviation)
Age [years]	54.8 ± 14.9	57.4 ± 10.8
Weight [kg]	82.7 ± 19.0	74.4 ± 12.2
Height [cm]	175.1 ± 8.7	171.2 ± 9.2
Male [%]	68	20
Albumin [g/dL]	3.7 ± 0.2	-
Creatinine clearance [ml/min]	105.6 ± 33.4	100.9 ± 24.2
Fraction unbound estimated [%]	0.71 ± 0.01	-
Administered Dose [g]	1.5 ± 0	1.5 ± 0
Infusion Duration [h]	i.v. bolus	i.v. bolus
Repetition every [h]	2.5	-

Table 1: Summary statistics of Patient characteristics; N = 25 Patients thorax surgery; N = 10 Patients with hand surgery

$$fu_i = \frac{1}{1 + \frac{[Albumin]_s}{[Albumin]_s} * \frac{(1 - fu_s)}{fu_s}}$$

Equation 1: fu_i = fraction unbound individual; fu_s= fraction unbound found in healthy adults; $[Albumin]_s$ = standard Albumin concentration in healthy adults

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

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

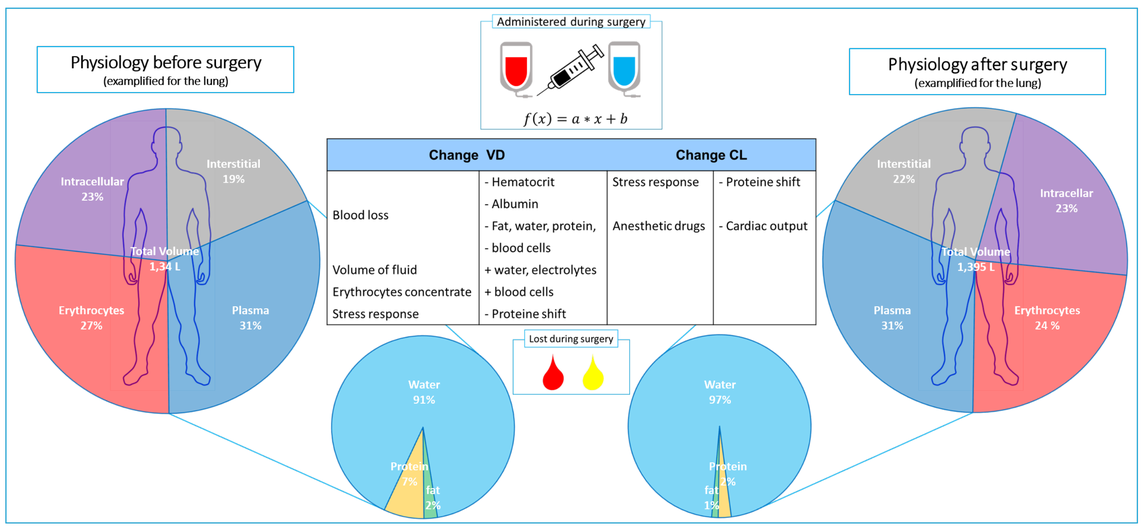

Figure 1: fu_i = fraction unbound individual; fu_s= fraction unbound found in healthy adults; $[Albumin]_s$ = standard Albumin concentration in healthy adults

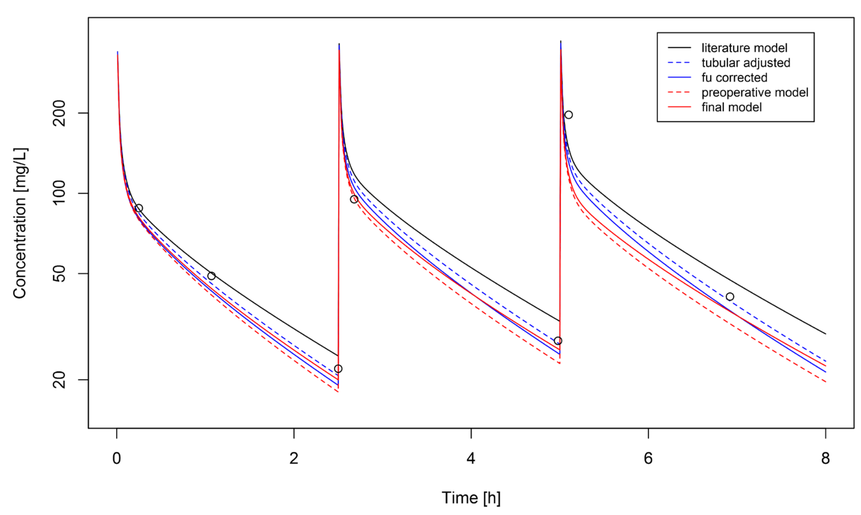

Figure 1: Plasma concentration changes over an 8 hour surgery; Circles are the measured plasma concentration

Results II:

By adjusting the partition coefficient and the endothelial permeability, the model describes the measured tissue concentration, with an MPE = 0.4% and MAPE = 34.5% accurately. All of the individual predicted values fall within 100% of the observed values. Within the population simulation based on the individual characteristics of our study group, 85.7% of the observed tissue concentration were in the range between 5% to 95% (almost 100% of the plasma concentrations). The re-evaluation of the scale up using the Function 2 lead to similar time curves, as described in Figure 2.

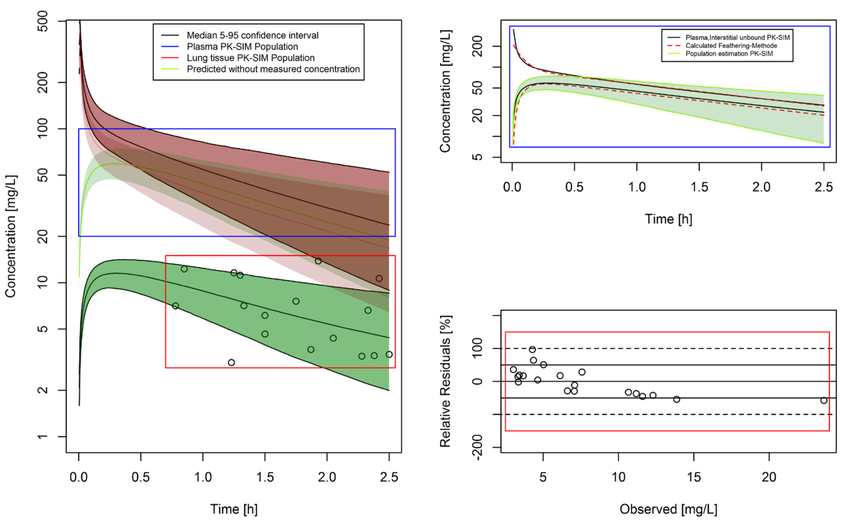

Figure 2: Left = Population simulation with the observed lung tissue concentration; right top = individual prediction described with Function 2 for lung interstital; right button = All individual predictions for lung tissue

Results I:

Without adjustment of the individual tubular secretion, just as described as an fix proportion ratio (55:45) a MPE and a MAPE from 13.6 and 31.9 was obtained. Using the individualized tubular secretion together with the adjusted individual albumin concentration resulted in an accurate fit for our “preoperation model”. The physiological changes during surgery, dominantly effecting the volume of distribution cause an under prediction of plasma concentrations (see Table 2 and Figure 1). Sensitivity analysis indicate a lower total clearance. We considered a decrease of 5 to 10 percent to readjust our final model. This value is also seen in the lower cardiac output, as also reported in the literature.

Model	MPE	MAPE
Literatur	13.6	31.9
Renal adjusted	8.1	31.0
Individual fu („preoperative“)	4.1	29.1
Physilogical changes	- 4.6	29.3
Total Cefuroxime clearance		
- 5 %	-1.7	29.0
- 10 %	1.4	29.0
- 20 %	8.4	29.5

Table 2: Prediction errors for each model calculated for each individual; MPE = mean prediction error; MAPE = mean absolute prediction error

Results III:

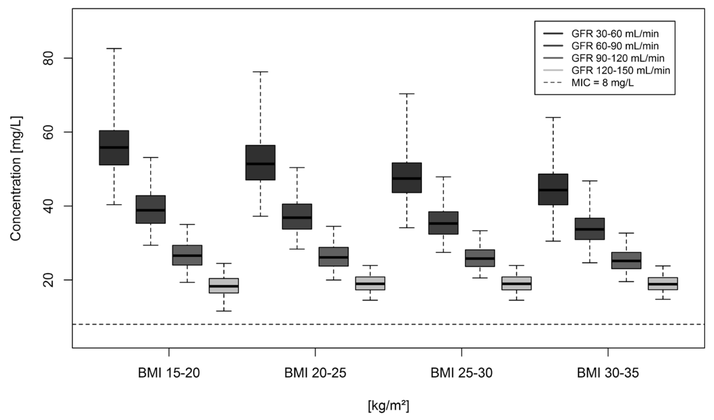

Figure 3: Boxplots describing the concentrations of the whole population after 70 % of the given dosing interval; Dotted line = MIC about 8 mg/L relevant for most pathogen species (EUCAST);

Simulations for the different BMI groups and kidney functions combined with the given dosing strategy resulted in adequate drug concentrations in the interstitial unbound compartment (Figure 4). To achieve maximal bactericidal effect, concentration of the free drug must exceed the MIC (8 mg/L) for 60-70% of the dosing interval [4]. Regarding the relevant interstitial unbound compartment a dosing regime of every 3 hours leads only in the first group (BMI 15-20 GFR 120-150 mL/min) to an undersupply of about 1-2% of the patients. In groups with lower GFR ≤ 90-120 ml/min a dosing regime of every 4 hours should also give adequate concentration levels. For renal impaired patients a single dose every 5-6 h should be sufficient.

Conclusions

We were able to predict the changes of the Pk triggered by surgery, as well as the lung tissue concentrations. There was no significant change of the PK triggered by a surgery, because two major effects antagonizing each other. The given dosing regimen lead to adequate interstitial unbound concentrations for all populations. Higher deviations in the group of small individuals with a high creatinine clearance were observed. Result III shows an option for longer dosing regimes, adapted to the kidney status of the individual.

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