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 physiologically-based pharmacokinetic (PBPK) model, using PK-Sim®/MoBi® [1].

Patients and Methods:

- **Software:**
  - PK-Sim®/MoBi®
- **Basis:**
  - Pharmacometric 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 (Michalama 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]

Results I:

Without adjustment of the individual tubular secretion, just as described as an fe proportion (55-65), 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.

Results II:

By adjusting the partition coefficient and the endothelial permeability, the model describes the measured tissue concentration, with an MPE = 6.4% 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.

Results III:

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 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 regime 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.