

Analysis of target-site distribution of meropenem in morbidly obese and non-obese patients using nonlinear mixed-effects modelling

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Background and Objectives

Meropenem (MER), a broad-spectrum β -lactam antibiotic, is used in calculated therapy and for the treatment of (multi-) resistant soft tissue infections, e.g. after surgery. Although obesity has been identified as a risk factor for surgical site infections [1], quantitative evaluation of pharmacokinetics (PK) of anti-infectives such as MER in obese patients is rare and often lacks crucial information on

exposure at the target-site, i.e. the interstitial space fluid (ISF) of subcutaneous (s.c.) adipose tissue. The aim of this analysis was to (i) quantify MER tissue distribution and elimination by developing a nonlinear mixed-effects (NLME) PK model based on concentrations both in plasma ISF, and (ii) identify patient-level characteristics which explain the variability in MER PK.

Methods

Pharmacokinetic data

Patients (Table 1):

- n=30 ($n_{\text{obese}}=15$, $n_{\text{non-obese}}=15$)
- Abdominal surgical intervention

Dosing:

- Infection prophylaxis before surgery
- Standard meropenem dosing (1000 mg 30-min i.v.)

PK sampling:

- Plasma concentrations** ($n=239$)
- Microdialysis (μD)** (interstitial space fluid (ISF) of s.c. adipose tissue)
 - Catheter 1 ($n=292$)
 - Catheter 2 ($n=293$)
- Retrodialysis**
 - Catheter 1 ($n=46$)
 - Catheter 2 ($n=45$)

Table 1: Summary of patient characteristics.

Patient characteristics		Non-obese patients, n=15	Obese patients, n=15
Sex, n (%)	Male	2 (13.3)	2 (13.3)
	Female	13 (86.7)	13 (86.7)
Age [years]	Median	50	52
	Range	31-64	30-65
BMI [kg/m ²]	Median	23.6	44.7
	Range	20.5-27.1	38.1-81.5
CLCR _{CG} [ml/min]	Median	76.0	99.4
	Range	53.6-136	51.3-188

BMI: Body mass index; CLCR_{CG}: Creatinine clearance estimated via the Cockcroft-Gault equation based on adjusted body weight.

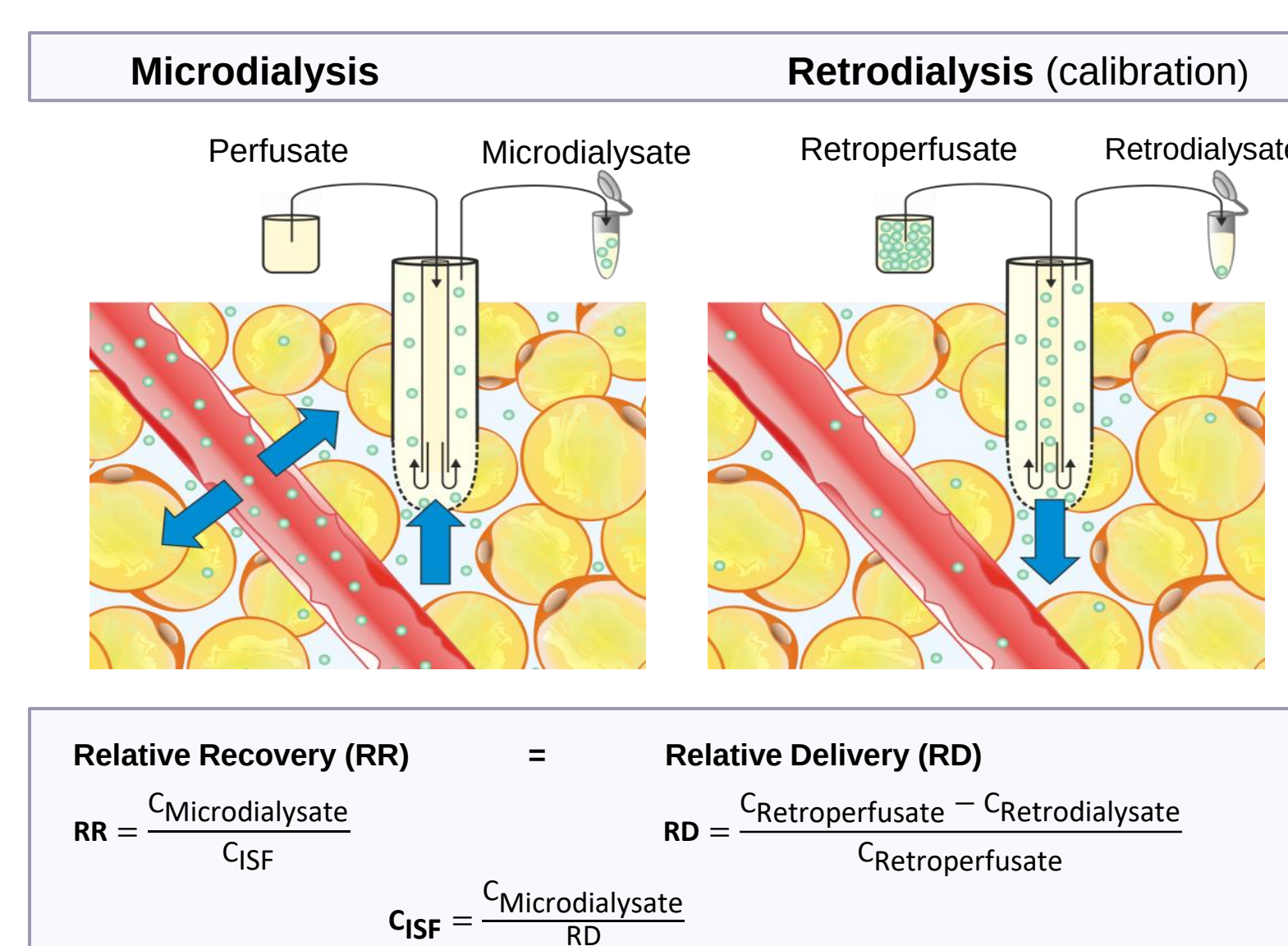


Figure 1: Principle of microdialysis (left) and retrodialysis (right) [2]. ISF: Interstitial space fluid; RD: Relative Delivery; RR: Relative recovery.

Model development

- An integrated NLME PK modelling approach was employed to simultaneously describe plasma and micro-/retrodialysis PK data of both catheters [3]
- Established covariate relationships such as effect of different body size descriptors and estimates of renal function on PK parameters were evaluated using e.g. theory based/empirical allometric scaling [4]
- Model adequacy was assessed by goodness-of-fit plots, likelihood-ratio testing, parameter precision and visual predictive checks
- Data analysis and modelling activities were performed using R 3.5.0, RStudio 1.1.447, NONMEM® 7.4.3 (FOCE+I) [5], PsN 4.6.0, Pirana 2.9.6, Xpose4 4.6.1 and Xpose 0.4.4

Results

- A catenary and mammillary three-compartment model (Figure 2) with μD observations related to a peripheral compartment described the observations equally well

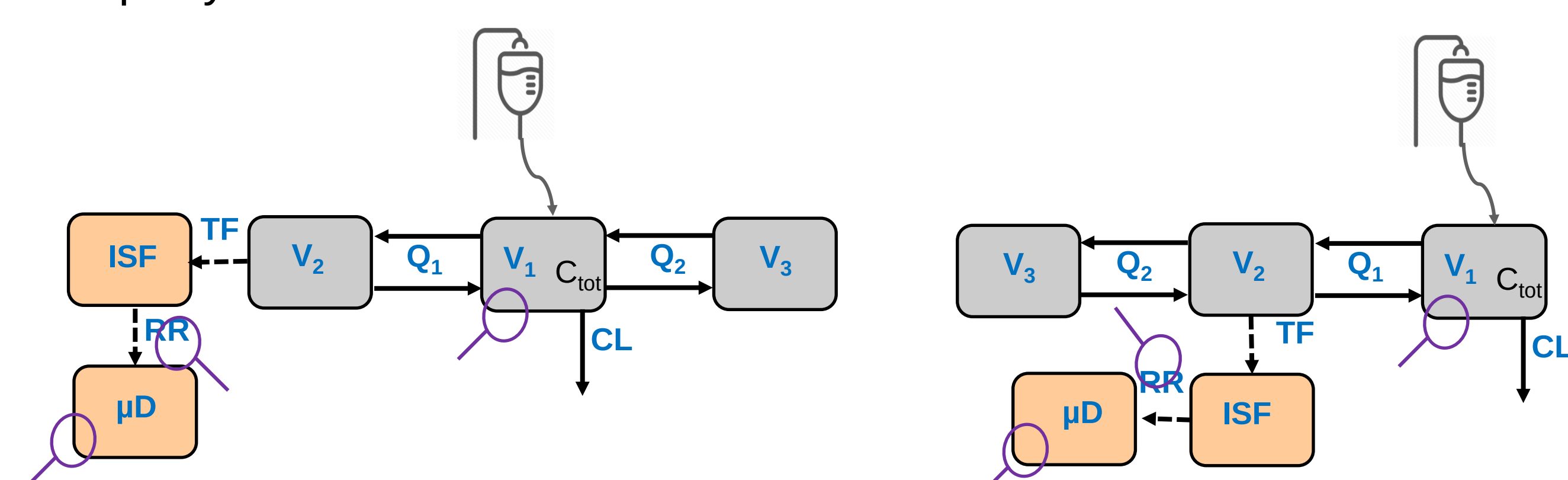


Figure 2: Integrated NLME mammillary (left) and catenary (right) PK model structure. Purple circles: observations. CL: Clearance, C_{tot} : Total meropenem plasma concentration; ISF: Interstitial space fluid of subcutaneous fat tissue, RR: Relative recovery; TF: Tissue factor relating peripheral concentration to ISF concentration; V_{1-3} : Central and peripheral volumes of distribution; $Q_{1,2}$: Intercompartmental CL; μD : Microdialysis integration compartment.

- AIC indicated better predictive performance of the catenary model compared to the mammillary model (Table 2) and was selected for further development

Results (cont.)

Covariate model development

- Theory-based allometry via adjusted body weight (ABW) markedly reduced interindividual variability (IIV) in the central and peripheral compartment (27% and 31% relative reduction, respectively), and explained parameter differences between obese and non-obese patients (Figure 3)
- CL was scaled using CLCR_{CG} and theory based allometry via ABW (Equation 1), which resulted in relative IIV reduction of 18% [4]
- Obesity status had an impact on relative recovery (-34.2% lower in the obese)

Equation 1: Scaling of meropenem clearance.

$$CL = TVCL_{\text{nonren}} \times \left(\frac{ABW_i}{ABW_{\text{med}}} \right)^{0.75} + TVCL_{\text{ren}} \left(\frac{CLCR_{CG,i}}{CLCR_{CG,\text{med}}} \right)$$

ABW_{med} : Individual/median adjusted body weight; $CLCR_{CG,\text{med}}$: Individual/median estimated creatinine clearance; $TVCL_{\text{nonren}}$: Typical fraction of CL scaling with ABW; $TVCL_{\text{ren}}$: Typical fraction of CL scaling with CLCR_{CG}.

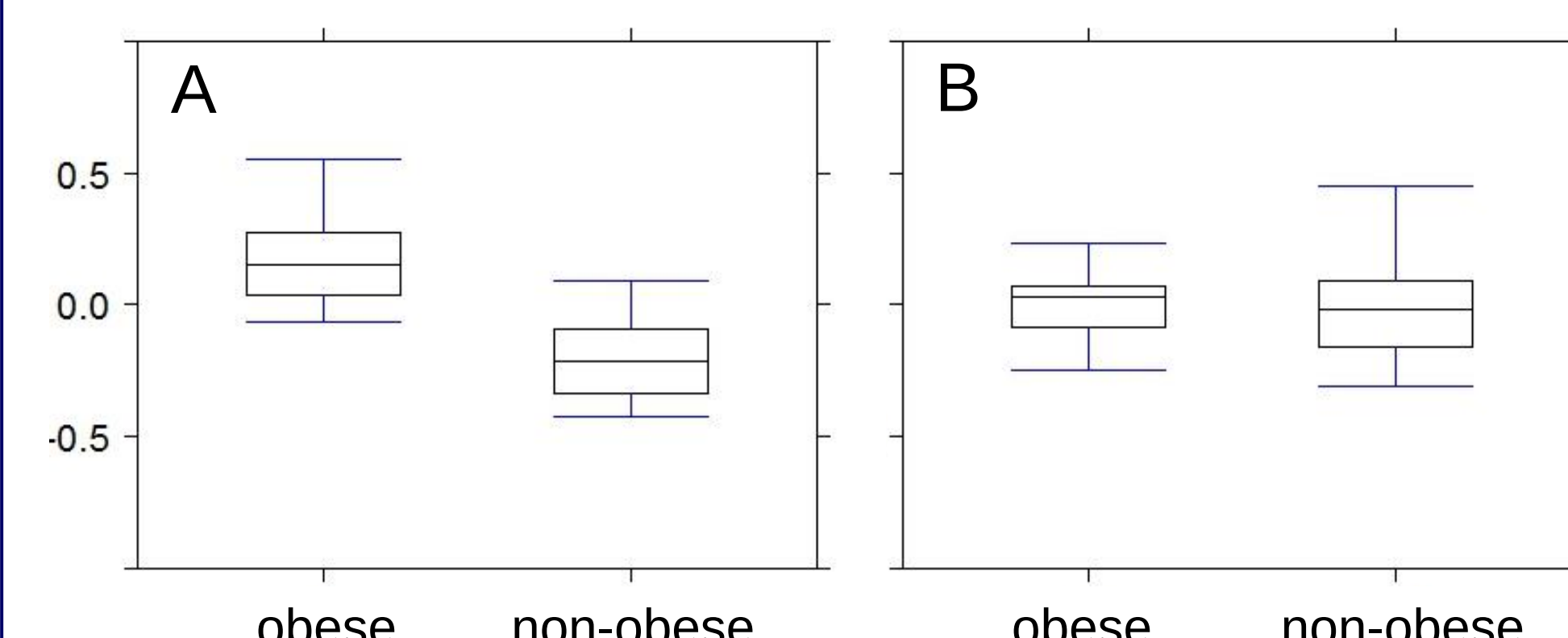


Figure 3: Distribution of the random effect on volume of distribution associated with interstitial space fluid before (A) and after allometric scaling (B). Boxes: Interquartile range (IQR), including median; whiskers (vertical lines): Range from box hinge, values within $\pm 1.5 \times \text{IQR}$.

- RR and TF were moderately correlated ($r = -0.53$); estimating the covariance between these two parameters resulted in improved model fit ($\Delta\text{OFV} = -19.7$)

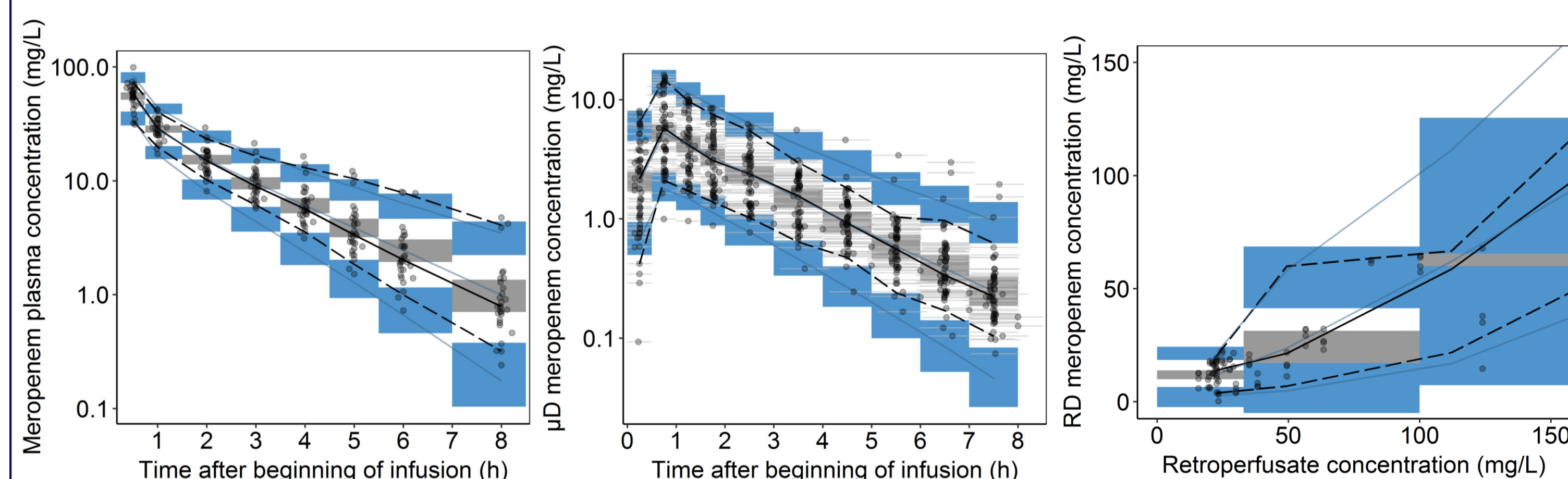


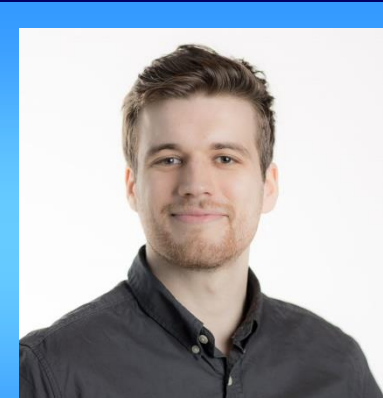
Figure 4: Visual predictive check of the population PK model after including covariate effects ($n=1000$). Grey circles: observations, Lines: 5th, 95th percentile (dashed), 50th percentile (solid) of the observed (black) and simulated (grey) data. Blue shaded areas: 95% confidence interval around simulated percentiles. Horizontal bars: length of microdialysis sampling interval. μD : microdialysis, RD: Retrodialysis.

Discussion and Conclusions

- A three-compartment catenary model was favoured over the mammillary PK model which likely reflected disposition from ISF into the cellular space
- Theory based allometry using ABW explained differences in PK parameters between obese and non-obese patients which could have important implications regarding adequate dosing of meropenem in the obese
- Next, a full covariate modelling approach will be used to analyse additional covariates such as haemodynamic markers

References:

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