Is a pooled population pharmacokinetic model predictive of plasma and microdialysate pharmacokinetics of linezolid in obese and non-obese patients?

Ehmann L. (1,2), Simon P. (3,4), Petroff D. (4,5), Minichmayr I.K. (1,2), Burau D. (1), Zeitlinger M. (6), Dorn C. (7), Huisinga W. (8), Wrigge H. (3,4), Kloft C. (1)

(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany,
(2) and Graduate Research Training program PharMetrX, Germany,
(3) Dept. of Anaesthesiology and Intensive Care Medicine , University of Leipzig, Germany,
(4) Integrated Research and Treatment Center (IFB), Adiposity Diseases, University of Leipzig, Germany,
(5) Clinical Trial Centre Leipzig, University of Leipzig, Germany,
(6) Dept. of Clinical Pharmacology, Medical University of Vienna, Austria,
(7) Dept. of Clinical Pharmacy, University of Regensburg, Germany,
(8) Institute of Mathematics, Universitaet Potsdam, Germany

Background and Objectives

Linezolid (LIN) is an oxazolidinone antibiotic exhibiting wide activity against gram-positive pathogens. Antibiotic concentrations at the site of infection are crucial for treatment success and can be obtained by the microdialysis sampling technique.

This work aims to investigate the applicability of a pooled population pharmacokinetic (PK) model [1] to predict plasma and microdialysis LIN data of a new population of obese and non-obese patients.

Methods

Pharmacokinetic data

- **Patients**:
  - n=30 (n_{obese}=15, $n_{non\text{-}obese}$=15)
  - Abdominal surgical intervention
- **Dosing**:
  - Infection prophylaxis before surgery
  - Standard linezolid dosing (600 mg 30-min i.v.)
- **PK sampling**:
  - **Plasma** (n=239)
    - Total concentrations (n=239)
    - Unbound concentrations (n=90)
  - **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=43)

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/m²]	*Median*	23.6	44.7
	Range	20.5-27.1	38.1-81.5
Surgical indications, n (%)	*Obesity*	-	15 (100)
	Cancer	10 (75)	-
	Others	5 (25)	-

Abbreviations: *BMI*: Body mass index

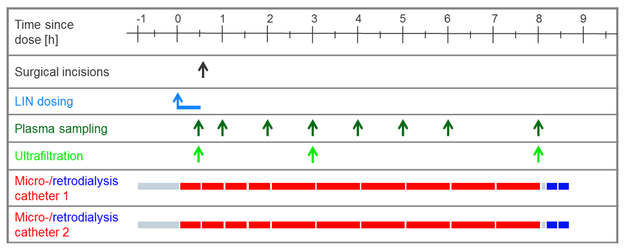


Figure 1: Study design and PK sampling schedule.
Abbreviations: LIN: Linezolid.

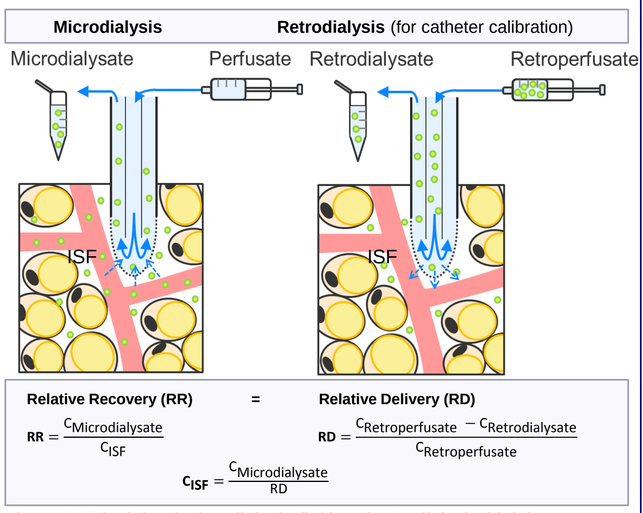


Figure 2: Principle of microdialysis (left) and retrodialysis (right).
Abbreviations: *ISF:* Interstitial space fluid; *RD:* Relative Delivery; *RR:* Relative recovery.

External model evaluation

- A pooled population PK model (Fig. 3, [1]) was evaluated for the applicability to predict plasma and micro-/retrodialysis PK data of catheter 1
- Concentration-time profiles of obese and non-obese patients were predicted using PK parameters estimated in the pooled population PK model based on an overweight diabetic (BMI_{median}=31 kg/m²) and a healthy population (BMI_{median}=23 kg/m²), respectively. Final model parameter estimates were used for Bayesian estimation of individual PK parameters (MAXEVAL=0 functionality in NONMEM)
- Model adequacy was assessed by goodness-of-fit plots, visual predictive checks and calculation of prediction errors (PE)

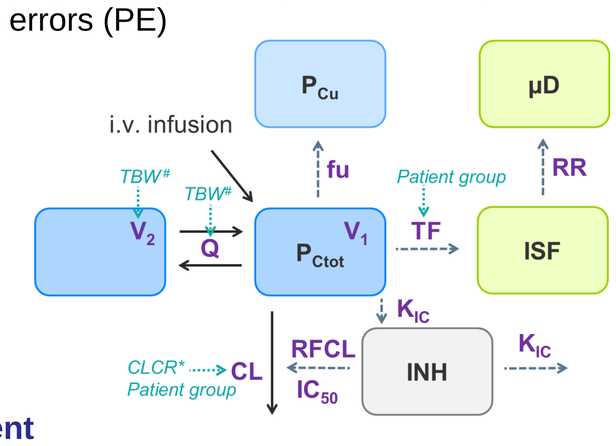


Figure 3: Schematic illustration of the pooled population PK model.
Colour coding: *Purple*: Fixed-effects model parameters; *Green*: Covariates (#allometric scaling, *linear covariate model).
Abbreviations: *CLCR*: Creatinine clearance estimated according to Cockcroft and Gault; *CL*: Clearance; *fu*: Fraction unbound; IC_{50}: Concentration in INH yielding 50% of CL inhibition; *INH*: Inhibition compartment; *ISF*: Interstitial space fluid of s.c. adipose tissue; K_{IC}: rate constant for the transfer into INH; P_{Ctot}: Total plasma concentration; P_{Cu}: Unbound plasma concentration; *Q*: Intercompartmental clearance; *RFCL*: Remaining fraction of CL at maximum CL inhibition; *RR*: Relative recovery; *TBW*; Total body weight; V_1: Central volume of distribution; V_2: Peripheral volume of distribution; *µD*: Microdialysate of subcutaneous adipose tissue.

Population PK base model refinement

- Several structural models were investigated (e.g. assigning µD data to separate compartments, to peripheral compartment of plasma data model)
- Model adequacy was assessed by goodness-of-fit plots, visual predictive checks and plausibility and precision of parameter estimated
- Data analysis and modelling activities were performed in NONMEM 7.3 (FOCE+I [2])

Results

External model evaluation

- Initial concentrations were less well captured than those measured in the elimination phase (Fig. 5, 6):
  - Overprediction in microdialysate
  - Underprediction in plasma

→ Distribution process not satisfactorily captured

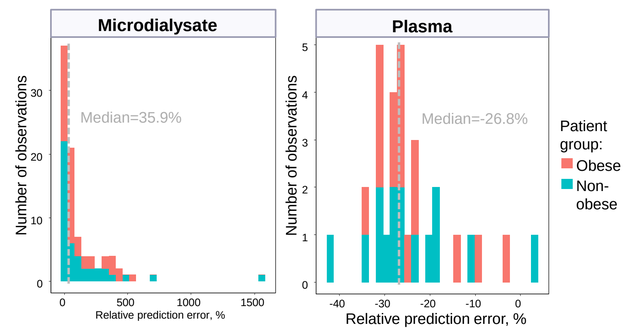


Figure 5: Distribution of prediction errors for microdialysate (t=0-1.5 h after infusion start) and **plasma** (t=0.5 h after infusion start) observations.

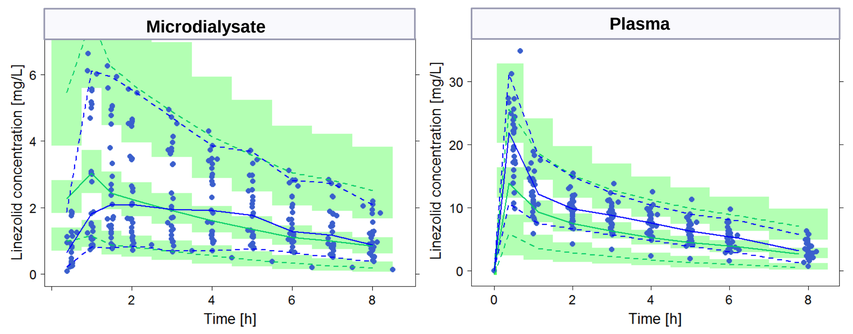


Figure 6: Visual predictive check of the refined population PK model (n=1000). *Blue circles*: observations, *Lines*: 5th, 95th percentile (dashed), 50th percentile (solid) of the observed (blue) and simulated (green) data. *Green shaded areas*: 95% confidence interval around simulated percentiles.

Population PK base model refinement

- Assigning the µD PK data to the peripheral compartment of the plasma data model (Fig. 5) improved the model predictivity (Fig. 7)
- The obesity status was found to significantly impact the relative recovery value and was therefore included as a covariate already in the base model (Tab. 2)

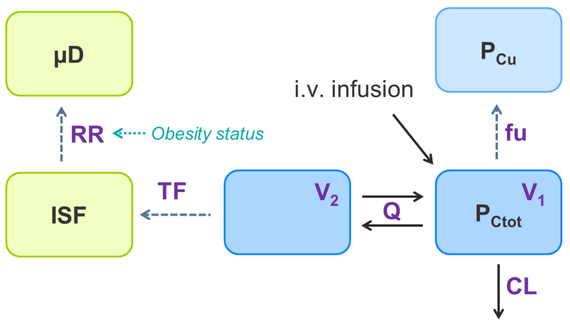


Figure 5: Refined population pharmacokinetic base model.
Colour coding and abbreviations see Figure 3.

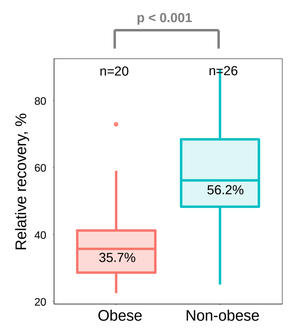
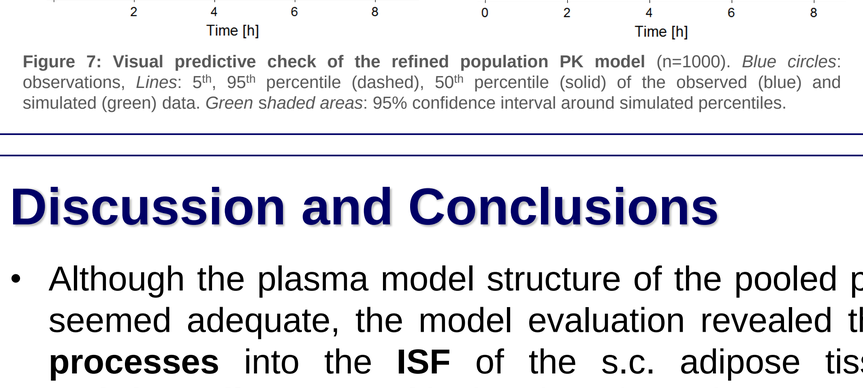


Figure 6: Box plots of all available relative recovery values in obese and non-obese patients.

Table 2: Parameter estimates of the refined population PK base model.

Parameter [unit]	Estimate (RSE%*)
Fixed-effects parameters	
Θ CL [L/h]	7.21 (6.4)
Θ V_1 [L]	18.4 (9.2)
Θ Q [L/h]	34.0 (11.7)
Θ V_2 [L]	20.1 (7.4)
Θ fu, %	84.0 (0.6)
Θ TF, %	48.1 (6.9)
Θ RR_{Obese}, %	35.8 (9.3)
Θ $RR_{Non\text{-}obese}$, %	56.6 (8.6)
Interindividual variability, CV%	
ω CL	35.9 (17.0)
ω V_1	47.8 (12.5)
ω Q	49.0 (17.5)
ω V_2	32.8 (17.8)
ω TF	29.9 (16.6)
ω RR	24.5 (22.0)
Residual variability, CV%	
σ P_{tot}	7.61 (9.2)
σ P_{unb}	6.14 (12.4)
σ µD	17.3 (8.7)
σ RD	17.3 (30.9)

Relative standard errors (RSE) of the random effect parameters are reported on approximated standard deviation scale; IIV was implemented assuming a log-normal distribution of the individual PK parameters. Abbreviations see Figure 3.



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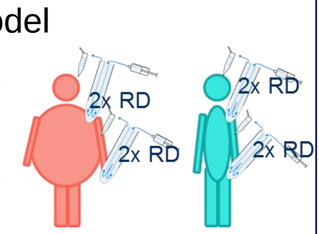
Discussion and Conclusions

- Although the plasma model structure of the pooled population PK model seemed adequate, the model evaluation revealed that the **distribution processes** into the **ISF** of the s.c. adipose tissue did **not** seem **satisfactorily captured** in the obese/non-obese population
- The structural **model** was **refined** by assigning the **ISF concentrations** to the **peripheral compartment** of the plasma data model
- Next, different sources of **variability** of the **microdialysis technique** (intracatheter, intercatheter, interpatient variability) will be evaluated, by including the PK data of microdialysis catheter 2 in the model



References:

[1] Minichmayr IK, Schaeftlein A, Kuti JL et al. Clin. Pharmacokinet. 56: 617-633 (2016).
[2] S.L. Beal, L.B. Sheiner, A.J. Boeckmann et al. NONMEM 7.3.0 User's Guides (1989-2013). Icon Development Solutions, Hanover, MD, USA.

For additional information, please contact
Lisa Ehmann,
lisa.ehmann@fu-berlin.de