Microdialysate-corrected mid-interval model versus microdialysate-based integral model – Population pharmacokinetics of levofloxacin in peripheral tissues

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Background and Objectives

Microdialysis (µD) has become the method of choice to determine unbound interstitial fluid (ISF) concentration especially of antiinfectives in peripheral tissues (PT) [1]. The interval based sampling method requires the correction of the measured microdialysate concentrations ($C_{\mu D}$) by the relative recovery (RR). The aim of this analysis was to compare two population PK modelling approaches with respect to descriptive and predictive performance for $C_{\mu D}$ of levofloxacin (LEV). A second objective was to investigate covariates (demographics, clinical chemistry, disease severity) on the PK of LEV, particularly those possibly effecting the distribution of LEV in ISF .

Materials and Methods

Patients/Study

- LEV measurements: Plasma and µD concentrations in adipose and muscle ISF (n=39, Tab. 1) from 5 clinical trials [2-4]
- Treatment: 500 mg LEV once daily
- Sampling scheme: rich data situation especially for the disposition phase (0-8 h) (Fig. 1)

Figure 1. Sampling scheme of LEV for plasma (n=39), ISF of adipose (n=34) and muscle thigh (n=18).

Table 1. Patients characteristics of n=39 study participants

Covariate	[Unit]	Median (range)*
Age	[y]	61 (23–89)
Sex	[% men]	82
Weight	[kg]	75.0 (51.0–120)
Height	[m]	1.70 (1.54–1.87)
Albumin	[g/L]	22.4 (18.0–57.0)
CLCR	[mL/min]	82.1(37.3–146)

*population: healthy volunteers (n=7), lung patients (n=5), septic patients (n=7), patients with coronary bypass (n=12) and soft tissue patients (SOFT)(n=8)

Population PK modelling approaches

Comparison of 2 approaches (Tab. 2) using NONMEM® 7.2:

- Microdialysate-corrected mid-interval (MCM) model: $C_{\mu D}$ corrected by RR prior to the data analysis, assigning the corrected $C_{\mu D}$ to the mid point of the sampling interval (Fig. 2)
- Microdialysate-based integral (MBI) model [5]: simultaneous analyses of RR and $C_{\mu D}$ data and assigns $C_{\mu D}$ as an integral over time to the end of the sampling interval (Fig. 2)

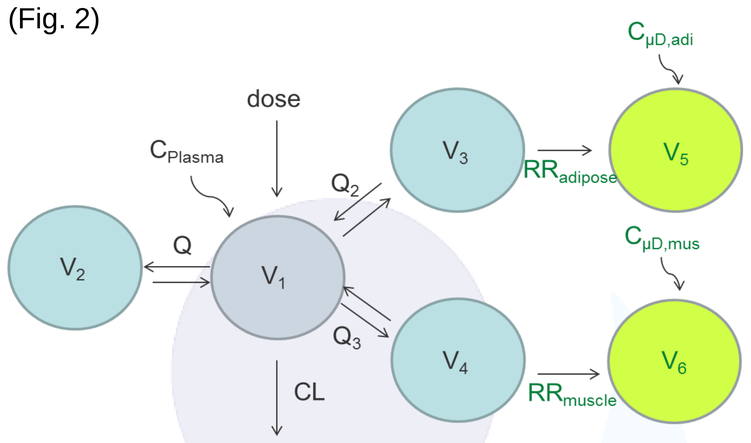

Figure 2. Microdialysate-corrected mid-interval (MCM) model (blue) and microdialysate-based integral (MBI) model (green) [5].

Selection criteria for the final base model:

- Akaike information criteria (AIC), plausibility and precision of parameter estimates, GOF plots and visual predictive checks (VPCs) (30th/70th percentile, n=1000)

Covariate selection based on:

- OFV, clinically relevant influence on the PK, ability to explain interindividual variability (IIV) on PK parameters.

Table 2. Comparison of the 2 investigated models

MCM Model	MBI model
• Data transformation prior to the data analysis → more assumptions and loss of information	• denotes the integral over the dialysate time interval → no assumption regarding time
• mid point of the sampling interval → error regarding the sampling time	• Simultaneous analysis of all measured data → Uncertainty and variability recognised

Results

- No difference between infected and healthy s.c. ISF were observed → pooling of the data in the model comparison possible (Fig. 3)
- PK parameter estimates of the MBI model were in better agreement with published ones [6], also revealing higher precision in comparison to the MCM model (Tab. 3)
- Lower AIC for MBI model (AIC: -1555) in comparison to MCM (AIC: 1582) model indicates a better model fit
- In contrast to the MCM model the MBI model adequately described the concentration-time profiles in both ISF of PT (Fig. 4)
- VPC (Fig. 5) demonstrated that predictive performance for MCM was worse for ISF_{muscle} , compared to the predictions of the MBI model
- Albumin (marker for the colloid osmotic pressure in the plasma compartment) significantly influenced intercompartmental CL (plasma to adipose ISF) explaining ~20% of IIV in CL (Tab. 4)

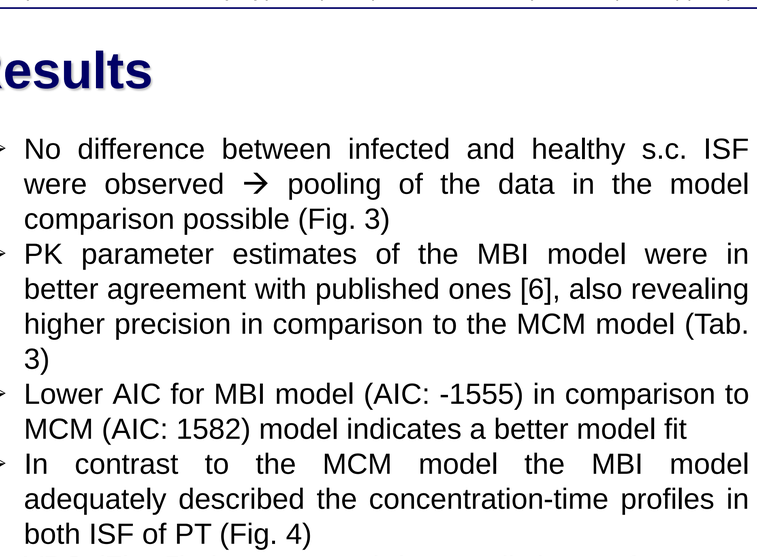

Figure 3. Concentration time profiles of LEV in different matrices.

- *Positive* covariate relation (7.54%/g/L) between albumin and Q2 indicated that albumin-dependent protein binding of LEV is negligible for the distribution of LEV
- Additionally CLCR being a marker for renal function and disease severity (septic>>soft tissue infections patients) showed an impact on CL of LEV explaining 20% of IIV (Tab. 4)

Table 3. Final parameter estimates of the MCM (upper panel) and MBI (lower panel) model. RSE% based on nonparametric bootstrap (n=1000). Green: Parameter estimates associated with the retrodialysate process.

Parameter [unit]		Estimate	%RSE	Parameter [unit]	Estimate	%RSE
Fixed-effects parameters				*Interindividual variability, %CV*		
CL	[L/h]	6.31	11	ωCL,	63.3	39
V_1	[L]	7.91	35	ωV_1	131	43
Q	[L/h]	71.7	27	ωV_2	42.4	55
V_2	[L]	46.0	19	ωV_3	75.5	55
Q_2	[L/h]	12.9	86	ωV_4	99.2	27
V_3	[L]	14.4	90	ωQ_2	121	38
Q_3	[L/h]	9.23	47	*Residual variability, %CV*		
V_4	[L]	16.7	56	σ_{prop}	32.4	14

Parameter [unit]		Estimate	%RSE	Parameter [unit]	Estimate	%RSE
Fixed-effects parameters				ωV_1	60.1	26
CL	[L/h]	6.78	6.9	ωV_2	82.8	34
V_1	[L]	16.9	10	ωV_3	73.7	38
Q	[L/h]	41.6	21	ωV_4	74.2	33
V_2	[L]	29.0	16	ωQ_2	104	43
Q_2	[L/h]	43.0	29	ωRR_{muscle}	41.8	28
V_3	[L]	15.9	27	$\omega RR_{adipose}$	50.2	22
Q_3	[L/h]	13.1	27	*Residual variability, %CV*		
V_4	[L]	18.7	28	$\sigma_{\mu D,adipose}$	28.2	17
RR_{muscle}		26.7%	7.4	$\sigma_{\mu D,muscle}$	25.8	19
$RR_{adipose}$		19.1%	5.9	$\sigma_{RR,adipose}$	18.2	29
Interindividual variability, %CV				$\sigma_{RR,muscle}$	25.4	22
ωCL		46.8	19	σ_{plasma}	10.2	11

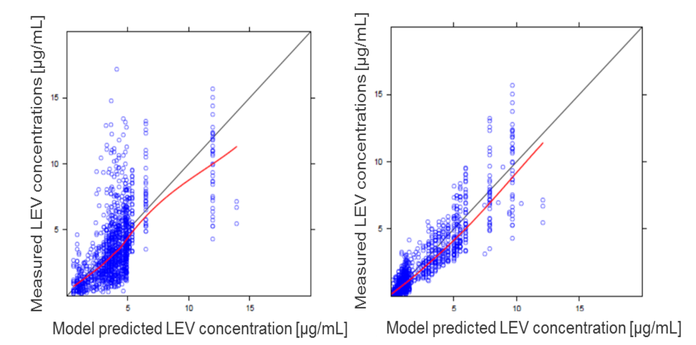

Figure 4. Goodness of fit of the MCM (left panel) and MBM (right panel) model

Table 4. Covariates meeting the selection criteria

Covariate relation	[unit]	Estimate	Explained IIV Absolute	Explained IIV Relative
CL_CLCR	1/mL/min	1.16%	11%	30%
CL_LUNG	-	-26.7%	9.0%	25%
CL_SEPS	-	-51.5%	9.0%	25%
CL_CBP	-	-17.8%	9.0%	25%
CL_SOFT	-	-7.44%	9.0%	25%
Q_2 _ALB	1/g/L	7.54%	20%	19%

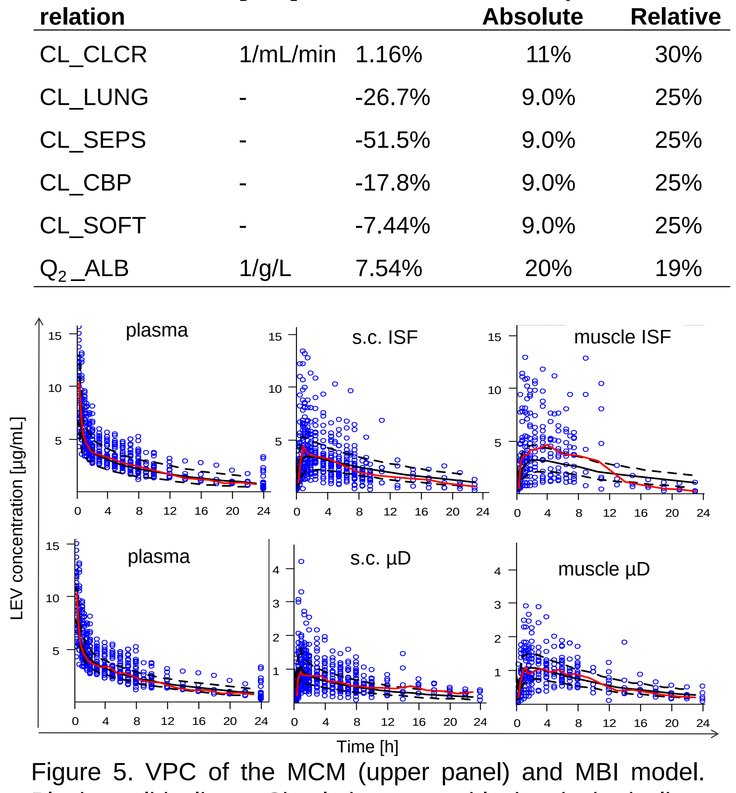

Figure 5. VPC of the MCM (upper panel) and MBI model. Black solid line: $Simulation_{median}$, black dashed line: $Simulation_{30th/70th\ percentile}$, red line: $Observations_{median}$, blue dots: Observations

References [1] Plock N et al. (2005), [2] Bellmann R et al. (2003), [3] Zeitlinger M et al. (2003), [4] Zeitlinger M et al. (2007), [5] Tunblad K et al. (2004), [6] Drusano GL. et al.(2002)

Conclusion

The MBI modelling approach showed the better descriptive and predictive performance compared to the MCM model and is therefore preferable for predicting additional non-investigated time-points or scenarios. This modelling approach enabled the **differentiation between µD-specific processes** (retrodialysis, µD) **and physiologically-based** (ADME, PBPK) **distribution of LEV in humans**. **Albumin-dependent binding of LEV is negligible** for the distribution of LEV in ISF of PT. Based on these results, more mechanistically-motivated models will be developed to explain the distribution of antiinfectives in ISF of PT.

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