Understanding variability in microdialysis measurements: introducing a combined calibration approach for piperacillin and tazobactam in LPS-induced septic piglets

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Background and Objectives

Inadequate target tissue fluid exposure may lead to treatment failure [1] in septic children → impact of **sepsis on tissue fluid exposure** in children **for piperacillin (PIP) and tazobactam (TAZ)** not investigated

Lipopolysaccharide (LPS) induced **septic piglet model** can elucidate impact of septic like state on drug disposition and pharmacokinetics

Microdialysis (µD): Gold standard method to obtain unbound drug **interstitial space fluid concentrations (C_{ISF})** [2], **reliable catheter calibration** is required for meaningful results

Catheter-specific calibration is commonly conducted by (i) **retrodialysis** (before/after dosing drug of interest) or (ii) an **internal standard** parallel to microdialysis sampling **(IS)**, with penicillin (PEN) used for PIP and TAZ [3]

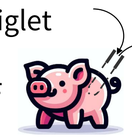
NLME methods are the **most adequate approach to handle µD-based data analysis** [4], IS calibration has never been included yet

We investigated the **feasibility** and potential **benefits** of both calibration methods individually and their combination leveraging µD-data from a **porcine animal study**

Methods

Calibration methods
- Retrodialysis (rD), Fig. 1
- Internal standard (IS)

Catheter insertion
- 1 catheter per piglet
- Into paraspinal musculature ISF



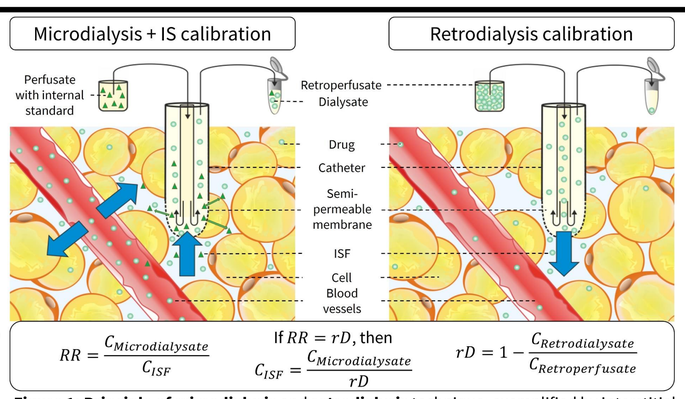


Figure 1: Principle of microdialysis and **retrodialysis** technique; exemplified by interstitial space fluid in adipose tissue.

Study design
Dosing (5 per period, tau 6 h)
- PIP 75 mg/kg; TAZ 9.375 mg/kg
- LPS infusion on day 3

Sampling after 1st and 5th dose (steady-state) per period

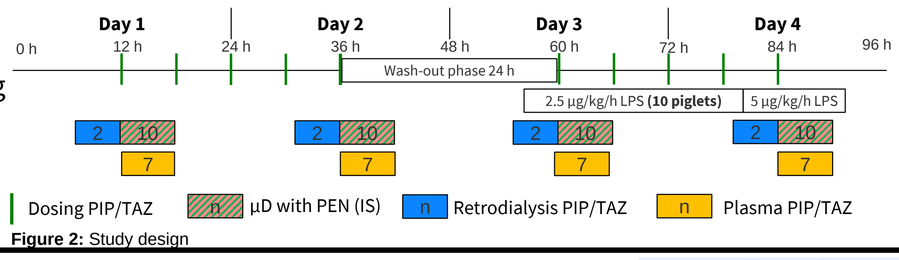


Figure 2: Study design

Modeling workflow:

1. Plasma submodel

2. µD-data integration
- Scm fwd/bwd (p-value 0.05/0.005)

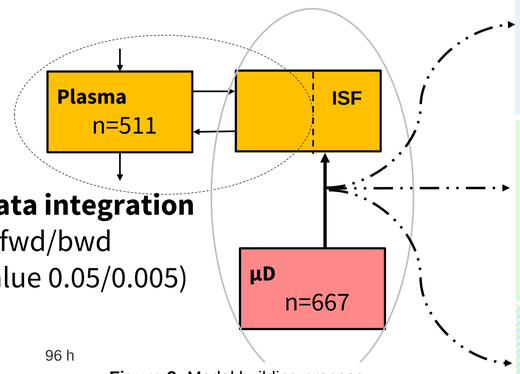
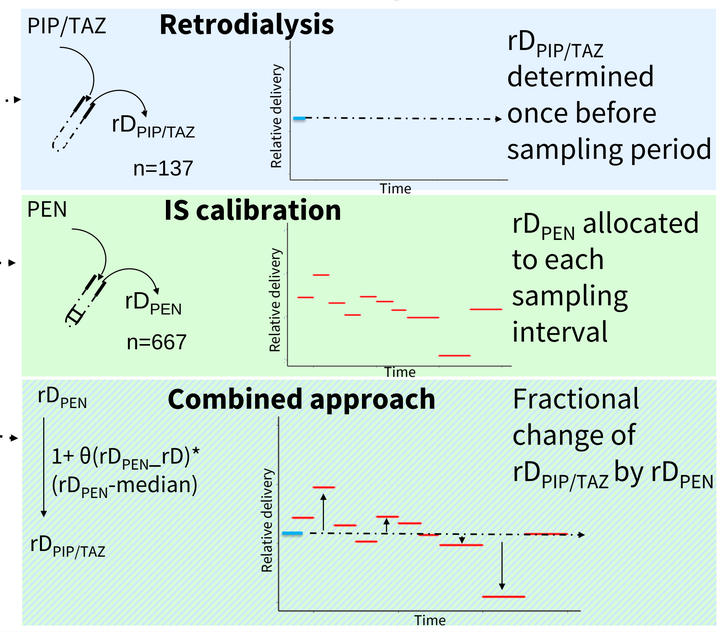


Figure 3: Model building process

Model evaluation:
- Parameter plausibility
- Variability reduction
- VPC (n=1000)

3. Calibration methods comparison



Results

Plasma model
- **Separate** models for PIP and TAZ (Figure 4)
- Retrodialysis as reference model
- **Covariates** to account for **septic-like state** included (Figure 4)
- Plasma-derived **PK parameters** (Table 1) **remained constant:** Change <10% compared to retrodialysis model
- RSE below <65%

Table 1: Plasma related model parameters for piperacillin and tazboactam from final retrodialysis model

Parameter [unit]	PIP estimates	TAZ estimates
CL [L/h]	4.01	5.90
V1 [L]	1.35	1.88
Q [L/h]	12.5	18.3
V2 [L]	1.62	1.80
IIV and IOV, %CV		
IIV on CL	10.0	8.38
IIV on V1	24.2	18.0
IOV on CL	15.7	9.40
Residual variability		
add C_{Plasma} [mg/L]	0.56	0.083
prop C_{Plasma} [CV,%]	16.5	17.0

Calibration
- Increased rD in control group over study days

→ Time effect on rD for control group:
- rD_{TIME} = (((Time)/40)**θ(Time_rD))
- Decreased rD in LPS septic like state (Figure 5)

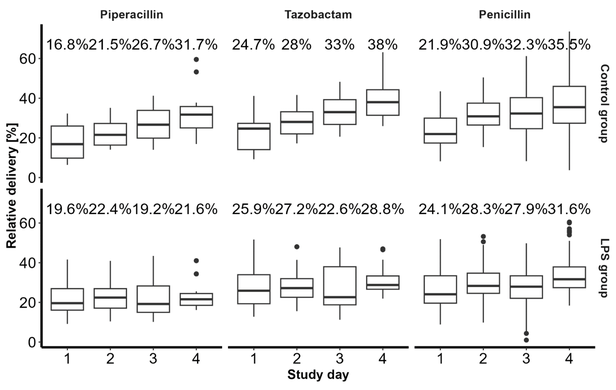
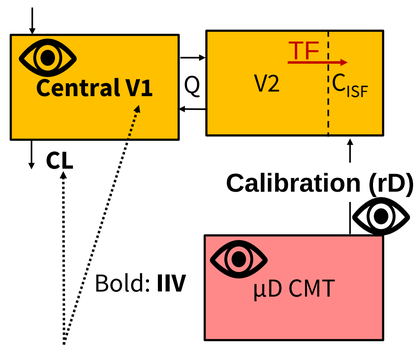


Figure 5: rD values over study days for piperacillin, tazobactam and penicillin per group with their medians



Covariates	Relation	PIP	TAZ
LEU on CL	power	0.450	-
TEMP on CL	linear	-0.054	-
WGT on CL	power	0.700	0.83
CRT on CL	power	-	-0.76
ALB on V1	power	-1.13	-0.91
LEU on V1	power	0.220	0.18
WGT on V1	linear	0.210	-

Figure 4: Final model structure for PIP and TAZ, inlcuding plasma and µD-data, and their covariate relations

Parameter [unit]	PIP estimates	TAZ estimates	PIP estimates	TAZ estimates	PIP estimates	TAZ estimates
	Retrodialysis		**IS calibration**		**Combined approach**	
rD [%]	23.2	29.4	**29.6***	29.5*	22.6	28.7
TF [%]	115	139	**88.3**	136	117	140
Time_rD	0.044	0.039	0.0013	0.0011	0.0241	0.026
rD_{PEN}–rD	-	-	-	-	**1.26**	**1.19**
IIV and IOV, %CV						
IIV on rD	14.5	12.0	10.4	8.5	**8.7**	**6.6**
IOV on rD	16.8	13.2	**20.3**	**19.4**	16.0	12.9
Residual variability						
prop µD[CV,%]	22.7	17.8	25.8	22.4	21.9	17.0
add µD [mg/L]	0.27	0.29	0.24	0.30	0.271	0.28
prop CrD [CV,%]	10.8	12.0	5.45	10.7	10.1	11.3

*rD_{PEN}

- No improvement in predictive performance
- Tissue factor compensates for changes in rD for PIP

- rD-related variability reduction by >40 %
- Reduction of time effect on rD

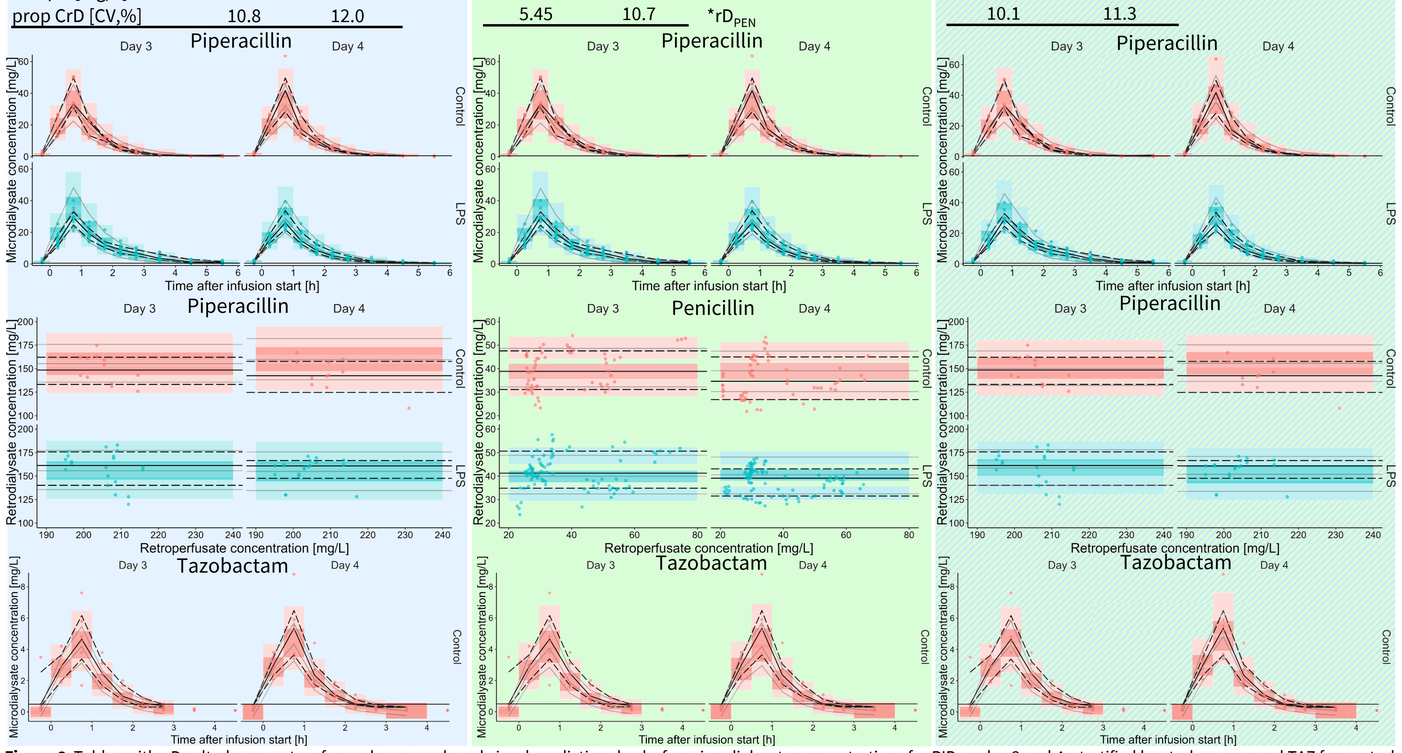


Figure 6: Tables with µD-ralted parameters for each approach and visual predictive checks for microdialysate concentrations for PIP on day 3 and 4, stratified by study group, and TAZ for control group, retrodialysate concentrations for PIP and PEN on day 3 and day 4 by study group based on simulations (n=1000) *Full Circles*: Observed drugs concentrations; *Lines*: 16th, 84th percentile (dashed), 50th percentile (solid) of the observed (black) and simulated (grey) data. *Orange shaded areas*: 95% confidence interval around 16th, 50th and 84th percentile of simulated data. **VPC shown when visible changes occured!**

Discussion and Conclusions

Retrodialysis calibration not considering physiological changes while sampling
→Assumption : Catheter extracts same fraction throughout entire sampling period

IS calibration: Drug-specific differences in rD compensated by TF
No improvement for PIP/TAZ in VPC or IIV
→Change in tissue exposure expected

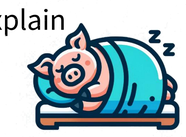
Benefits **combined calibration** approach
- **Individual drug-specific rD** for each sampling interval
- **Variability** between samples **explained by IS**

- Improved **predictive performance** in control group
- **Reduction of rD-related IIV**
- **Reduction rD-related time dependency**

- **Feasible and beneficial**

Changing **blood flow** though pigs' **activity** could explain
1) Increase of general rD over days
2) Variability in rD_{PEN} over time

→ **Blood flow** and **activity** should be **monitored**



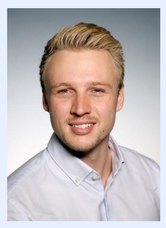
IS calibration in combination with retrodialysis explained *in vivo* observed rD-related variability, thus improves understanding and interpretation of µD data

References

[1] C. Fleischmann-Struzek et. al, Lancet Respir Med, 2018
[2] N. Plock et. al, Eur. J. Pharm. Sci., 2005
[3] M.B. Knudsen et. al, J. Pharm. Sci. 2021
[4] D. Busse et. al, Pharm.Res., 2021

Abbreviations

Add: additive; ALB: Albumin; CL: Clearance; CRT: Creatinine IIV: Interindividual variability; IOV: Inter-occasional variability; ISF: Interstitial space fluid; LEU: Leucocytes; LPS: Lipopolysaccharides; PIP: Piperacillin; PEN: Penicillin; prop: proportional RR: Relative recovery; rD: Relative delivery; TAZ: Tazobactam; PEN: Penicillin; TEMP: Temperature; Time_rD: Time effect on rD; rD_{PEN}–rD: fractional change of rD based on IS calibration; V: Volume of distribution; VPC: Visual predictive check; WGT: Body weight; µD: Microdialysis



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