

Determination of recovery and optimal calibration technique for piperacillin-tazobactam: An *in vitro* microdialysis study

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BACKGROUND

Research on the tissue disposition of antibiotics is scarce in children.



(dialysate)

perfusate

METHODS

The *in vitro* experimental set-up consisted of three 63 Microdialysis catheters at a perfusion flow rate of 2 µL/min. The GR and LR were determined in the context of three PTZ concentrations (20/2.5, 50/6.25 and 200/25 µg/mL) and at three different time points (0-30 min, 30-60 min, 60-90 min). Penicillin (50 µg/mL) was selected as internal calibrator for PTZ. A GR of at least 20% is recommended to be able to obtain reliable results in *in vivo* studies. The LR of PTZ (RDdrug) and PEN (RDcal) ideally do not differ from the GR of PTZ.

Microdialysis is the currently gold standard for measuring unbound drug concentrations in the interstitial fluid of tissue. In microdialysis, a small probe consisting of a semipermeable hollow fiber membrane is implanted into the target tissue. The fraction of the drug in the interstitial fluid that actually crosses the membrane is called the relative recovery or GR. Different calibration methods can determine the magnitude of this GR. Preceding in vivo studies, an in vitro phase is needed to finetune several experimental factors to ensure optimal GR.

RESEARCH QUESTIONS

- Is MD a reliable measuring technique for PTZ?
- Are RDdrug and RDcal suitable calibration techniques for PTZ?



This figure¹ illustrates net diffusion of the drug of interest (*open circles*) into the probe (GR), and the net diffusion of the calibrator (*closed circles*), from the probe to the extracellular space (LR). By measuring the LR of the calibrator you can estimate the GR of the drug of interest. The calibrator is the drug itself (during RDdrug) or a very similar compound (RDcal).

GLOSSARY

MD	microdialysis			
GR	gain rate			
LR	loss rate			
RDdrug	retrodialysis by drug			
RDcal	retrodialysis by internal calibrator			
PTZ	piperacillin-tazobactam			
PIP	piperacillin			
TAZ	tazobactam			
PEN	penicillin G			

RESULTS

Suitability of the calibration techniques

	GR PIP	LR PIP	LR PEN	P value		
RDdrug	43.80 %	47.33 %		P = 0.059		
RDcal	43.80%		52.11%	P < 0.001		
	GR TAZ	LR TAZ	LR PEN	P value		
RDdrug	55.82 %	58.83 %		P = 0.131		
RDcal	55.82 %		52.11%	P < 0.001		
Table: comparison of the mean GR and LR of PIP, TAZ and PEN.						

The small differences between GR and LR of PTZ and PEN are of little clinical relevance as the MD technique in itself already exhibits a high intrinsic variability that exceeds the differences found in this study.

Concentration and time dependency The drug concentration and time point of



measurement did not influence the GR and LR of PTZ.

Graph: GR and LR of PTZ and PEN, displayed as mean (black dot) and range (bar)

CONCLUSIONS

- MD is a reliable measuring technique for PTZ : The GR of PTZ is sufficiently high and not influenced by time or drug concentration.
- Both RDdrug and RDcal can be used as calibration methods for PTZ.
- These results can be applied in clinical microdialysis research investigating the tissue disposition of PTZ.

REFERENCES

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